PERSPECTIVE

Mismatch repair, molecular switches, and signal transduction

Richard Fishel¹

Genetics and Molecular Biology Program, Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania 19107 USA

The foundation of molecular switches in biology is grounded in translation elongation and cellular signal transduction. In these systems, guanine nucleotide-bound proteins (G proteins) produce the ON and OFF signaling states that act as gates for downstream biochemical processes. Recent studies on the human mismatch repair reaction have suggested a similar molecular switch that relies on adenine nucleotide-bound forms (A proteins) to produce an ON and OFF signaling state. In the field of signal transduction, the concept of a molecular switch is elementary whereas the biochemical processes of DNA repair appear foreign. Similarly, the field of DNA repair recognizes the complex machinery required for DNA manipulation events but regards biochemical signaling processes as essential cellular input but outside the genome juggernaut. The concept of a molecular switch as an integral step in mismatch repair should accelerate communication between these two fields toward a resolved and unified mechanism for biological signaling processes.

Genetics of mismatch repair

There are at least three ways in which mismatched nucleotides arise in DNA: (1) physical or chemical damage to the DNA and its precursors, such as deamination of 5-methyl-cytosine (Friedberg 1990); (2) misincorporation of nucleotides during DNA replication can yield mismatched base pairs as well as the insertion and deletion of nucleotides (for review, see Kolodner 1996; Modrich 1989, 1997); and (3) genetic recombination produces regions of heteroduplex DNA that may contain mismatched nucleotides when such heteroduplexes result from the pairing of two different parental DNA sequences (Holliday 1964). Mismatched nucleotides produced by each of these mechanisms are known to be repaired by enzyme systems that are both specific and overlapping (Friedberg 1990).

The most extensively studied system for mismatch repair (MMR) is the DNA adenine methylation (Dam)-instructed pathway of *Escherichia coli* (for review, see Modrich 1989; Modrich and Lahue 1996). The Dam-in-

structed pathway promotes a long-patch (~2 kb) excision repair reaction that is dependent genetically on the *mutH*, *mutL*, *mutS*, and *mutU* (*uvrD*) gene products. Discrimination of the newly replicated DNA strand from the original template DNA strand is dependent on transient undermethylation of the adenine nucleotide within a GATC Dam sequence. The MutHLS pathway appears to be the most active MMR pathway in *E. coli* and is known to both increase the fidelity of DNA replication as well as to act on recombination intermediates containing mispaired bases (Fishel and Kolodner 1983; Fishel et al. 1986).

Homologs of the prokaryotic MutS and MutL proteins have been identified in nearly every organism with the exception of Archaea (for review, see Kolodner 1996; Fishel and Wilson 1997). At present there are 41 MutS homologs and 21 MutL homologs in the NCBI database. In *Saccharomyces cerevisiae*, six MutS homologs (MSH1–MSH6) and three MutL homologs (MLH1, MLH2, PMS1) have been identified, whereas in human cells a nearly identical set of five MutS homologs (hMSH2–hMSH6) and three MutL homologs (hMLH1, hPMS1, and hPMS2) are known (Fujii and Shimada 1989; Kramer et al. 1989; Linton et al. 1989; Mankovich et al. 1989; Reenan and Kolodner 1992; Fishel et al. 1993; New et al. 1993; Bronner et al. 1994; Burns et al. 1994; Nicolaides et al. 1994; Prolla et al. 1994; Hollingsworth et al. 1995; Palombo et al. 1995; Acharya et al. 1996). Yet, outside of Gram-negative bacteria, there do not appear to be homologs of MutH. Thus, the mechanism of strand discrimination in even close relatives of *E. coli*, the gram-positive bacteria, remains a mystery. The multiple MutS and MutL homologs have been found to participate in the diverse activities of nuclear (MSH2, MSH3, MSH6, MLH1, PMS1) and organellar (MSH1) postreplication mismatch repair as well as distinct meiotic functions (MSH4, MSH5) (Kolodner 1996; Fishel and Wilson 1997).

Biochemistry of mismatch repair

Purification and reconstitution studies by Modrich and colleagues have led to a biochemical model for postreplication mismatch repair in *E. coli*. The reconstituted

¹E-MAIL rfishel@hendrix.jci.tju.edu; FAX (215) 923-1098.

system requires the MutH, MutL, MutS, and UvrD (helicase II) proteins along with DNA polymerase III holoenzyme, DNA ligase, single-stranded DNA binding protein (SSB), and one of the single-stranded DNA exonucleases, Exo I, Exo VII, or RecJ (Lu et al. 1983; Su and Modrich 1986; Welsh et al. 1987; Grilley et al. 1989; Lahue et al. 1989; Cooper et al. 1993). In this widely held biochemical model, initiation of a MMR event occurs when MutS recognizes and binds mispaired nucleotides that result from polymerase misincorporation errors (Su and Modrich 1986). It is then suggested that MutS mismatch binding is followed by interaction with the MutL protein (Grilley et al. 1989), which has been proposed to accelerate an ATP-dependent translocation of the MutS–MutL complex (Allen et al. 1997) to a hemimethylated GATC Dam site bound by MutH (Welsh et al. 1987). The MutS–MutL complex then stimulates an intrinsic endonuclease activity of MutH, which results in a specific strand scission on the unmethylated, newly replicated DNA strand (Lahue et al. 1987; Welsh et al. 1987; Cooper et al. 1993). This strand scission directs one of three single-stranded exonucleases (Rec J, Exo I, Exo VII) to degrade the newly replicated strand, which is then re-synthesized by the Pol III holoenzyme complex (Lahue et al. 1989). The net result is a strand-specific mismatch repair event that can be bidirectional. Many of the genetic studies performed with this system appear to support this biochemical interpretation. For example, *mutH*, *mutL*, and *mutS* bacteria exhibit a mutator phenotype that is presumed to be the result of the increased probability of misincorporation errors leading to mutations (Demerec et al. 1957; Miyake 1960; Siegel and Bryson 1967; Hill 1970). However, not all predictions arising from this model agree with the genetic results. For example, *recJ* *exoI* *exoVII* bacteria do not appear to exhibit a mutator phenotype (Harris et al. 1998), suggesting that there may be other exonuclease(s) or mechanism(s) involved in the mismatch repair process.

Unique functions for the mismatch repair proteins

The most obvious unique function for mismatch repair proteins is the specific mispair binding activity ascribed to MutS homologs (Su and Modrich 1986; Fishel et al. 1994; Chi and Kolodner 1994; Drummond et al. 1995;

Acharya et al. 1996; Marsischky et al. 1996; Gradia et al. 1997). A clear function of the MutL homologs has not yet been identified. Classification of MutS and MutL homologs is based on the recognition of highly conserved regions of amino acid identity. The most highly conserved region of the MutS homologs is confined to a region of ~150 amino acids that encompass a helix–turn–helix (HTH) domain associated with a Walker-A adenine nucleotide and magnesium binding motif (Walker et al. 1982). This adenine nucleotide binding domain constitutes 100% of the identity between the known MutS homologs (Fishel and Wilson 1997; Fig. 1). Purified bacterial, yeast, and human MutS homologs have been found to possess an intrinsic low-level ATP hydrolysis (ATPase) activity (Haber and Walker 1991; Chi and Kolodner 1994; Alani et al. 1997; Gradia et al. 1997). This ATPase activity is likely to be important for the function of the MutS homologs because mutation of a conserved lysine residue in the adenine nucleotide binding domain results in a dominant mutator phenotype in both bacteria and yeast (Haber and Walker 1991; Alani et al. 1997). As suggested above, the most widely held model for MMR suggests that MutS mispair binding is followed by MutL association, which then results in an energy-dependent translocation of this complex to a hemimethylated Dam site that is occupied by the MutH protein. In retrospect, this appears to have been a simplistic view because the rate of ATP hydrolysis ($k_{\text{cat}} \approx 10 \text{ min}^{-1}$) is unlikely to be sufficient to drive mechanical translocation the several hundred to thousand nucleotides (on average) required to encounter a MutH bound hemimethylated site. For example, if one ATP was required to translocate one nucleotide (as the most well-accepted mechanism would suggest), then it would take 25–100 min to encounter a MutH on average. Yet, remethylation of the transiently hemimethylated Dam sites has been found to occur within 0.1–3 min of the passing replication fork (Campbell and Kleckner 1990). Although the ATPase activity could in theory be significantly faster in vivo, no stimulatory factor has been identified to date despite an extensive search. In addition, the prevailing mechanism does not adequately account for MutL function nor the highly conserved domains recognized between MutL homologs from bacteria to man (regions containing 100% identity in 21 homologs).

Figure 1. Homology spectrum of 35 MutS homologs. Protein alignment was performed using Megalign (DNASTAR, Madison, WI). Alignments were colored (DNASTAR, Madison, WI) to indicate 20% (7/35 amino acid identity at an aligned amino acid position), up to 100% (35/35 amino acid identity). The consensus ATP binding domain (ATP) and HTH are shown. The initial alignment included 11 prokaryotes and 9 eukaryotes. Whereas the prokaryotes generally contribute one MutS homolog, eukaryotes may contribute up to six different MutS homologs (Fishel and Wilson 1997).

The hMSH2-hMSH6 molecular switch

Last year we proposed that the human MutS homologs, hMSH2-hMSH6, function as a molecular switch responsible for the timing of mismatch repair (Gradia et al. 1997; Fig. 2A,B). This hypothesis was based on the observations that: (1) The ADP-bound form has a high affinity for mismatched nucleotides; (2) the exchange of ADP for ATP results in the release from the mismatch in the absence of hydrolysis; (3) release appears to occur by simple dissociation and/or hydrolysis-independent diffusion off the ends of the short oligonucleotides used in these experiments; and (4) hydrolysis of ATP results in recovery of the mismatch-binding competent ADP-bound form. The rate-limiting step and the ultimate control of the hMSH2-hMSH6 molecular switch is likely to be the ADP → ATP exchange, which is exceedingly inefficient in the absence of a mismatched nucleotide. The characteristics of the hMSH2-hMSH6 switch appear most similar to the G-protein mediators of seven-transmembrane (7-TM) domain receptor signaling such as that used by the β -adrenergic and rhodopsin receptors (Fig. 2C), as well as the prototypical oncoprotein/G-protein Ras (Fig. 2D; Tocque et al. 1997). More specifically, the observation that hMSH2-hMSH6 is induced to exchange ADP for ATP in the presence of a mismatched nucleotide and then dissociates from the mismatch to transduce a signal, mirrors ligand binding by 7-TM receptors, which induce the associated G protein to exchange GDP for GTP and then the GTP-bound form dissociates from the receptor to transduce a signal.

These similarities allowed us to develop two related models for mismatch repair that are fundamentally different from all previously suggested mechanisms. These models are both based on the concept that MutS and its homologs are a novel type of molecular switch that determines the timing and/or appropriate assembly of repair components. The apparent affinity of hMSH2-

hMSH6 for mismatched nucleotides ($K_d \approx 2\text{--}20\text{ nM}$) has suggested that a single mismatch in a human cell should be recognized efficiently and bound. Furthermore, this binding is stabilized slightly in the presence of ADP. We propose two nonexclusive models: In the first model, tight binding to mismatch nucleotides by the ADP-bound form of hMSH2-hMSH6 acts as a flag for the assembly or nearby localization of the excision repair machinery. When the complete system is assembled, then exchange of ADP for ATP would be triggered and hMSH2-hMSH6 would be released from the mismatch (Fig. 2A); thus signaling exonucleolytic excision and re-synthesis of the region containing the mismatched nucleotide. Once released from the mismatched nucleotides, the intrinsic ATPase activity of hMSH2-hMSH6 would hydrolyze the bound ATP, resulting in a form that is once again competent for mismatch binding (Fig. 2A). In the second model, recognition of a mismatched nucleotide provokes the ADP → ATP nucleotide exchange and hydrolysis-independent, DNA-associated diffusion of hMSH2-hMSH6 away from the mismatch to the assembled (or partially assembled) mismatch repair components (Fig. 2B). Activation of these components by the confederation of this ATP-bound form of hMSH2-hMSH6 either engages the repair process (signaling the timing of mismatch repair as above) or allows the appropriate assembly of the remaining mismatch repair machinery. This activation event would result in the release of hMSH2-hMSH6, hydrolysis of ATP, and recycling of the mismatch competent form (Fig. 2B). The advantage of this latter model is that the hMSH2-hMSH6 remains associated with the DNA in an activated-form poised to transduce the mismatch signal to any nearby mismatch repair components.

As a free protein complex, hMSH2-hMSH6 does not efficiently exchange the ADP remaining after hydrolysis, providing a long-term mismatch-recognition-competent molecule. Again, this ADP-mismatch-bound and ATP-

Figure 2. Comparison of the hMSH2-hMSH6 molecular switch with G-protein switches. (A) The hMSH2-hMSH6 simple-dissociation molecular switch; (B) the hMSH2-hMSH6 hydrolysis-independent translocation molecular switch; (C) the heterotrimeric G-protein molecular switch; (D) the Ras G-protein molecular switch.

mismatch-released switch appears functionally equivalent to the 7-TM G-protein switches in that a signal is transduced to downstream factors when the NDP is exchanged for the NTP and the G protein dissociates from the 7-TM receptor. The key difference in the mismatch repair models described above and those previously proposed, is the concept that ATP hydrolysis is not required to physically transduce the mismatch binding signal to the downstream machinery, but instead is required to recycle the recognition system. Furthermore, in these models the *authentic signal* is the *conformational transition* that ATP binding induces in the MutS homologs hMSH2-hMSH6; thus, the concept of a molecular switch.

Switches in signal transduction

G proteins are the prototypical biological switches (for review, see Sprang 1997 and references therein). Historically, the first recognized G protein was the *E. coli* EF-Tu subunit, which promotes the correct positioning of an aminoacyl-tRNA on an mRNA within the ribosome (Keller and Zamecnik 1955; Nathans et al. 1962). As the process of protein synthesis proceeds, a more classic switch reaction occurs when a second G protein, EF-G, binds to GTP and signals the translocation of a growing peptidyl-tRNA from the A site to the P site, prior to EF-Tu recruitment of the next aminoacyl tRNA. The hydrolysis of the bound GTP by EF-G is used to recycle/reset the system. However, it was the Ras oncogene that focused attention on the function of G proteins (Fig. 2D) (Weinberg 1989). In general, G proteins use the binding energy of GTP to stabilize “switch regions” in conformations that will permit their association with effectors, and the hydrolysis of $\text{GTP} \rightarrow \text{GDP} + \text{P}_i$ is used to reset the switch. Mutagenesis and X-ray crystallography studies have identified five protein regions (G domains) that contact the GTP at points around the nucleoside rings and along the length of the phosphate chain (Sprang 1997). Two of those G domains include the Walker A and B motifs (Walker et al. 1982). Furthermore, there are at least two switch regions (switch I and II) that undergo conformational transitions in response to nucleotide binding and hydrolysis have been identified in all of the G proteins with known crystal structure (Sprang 1997). Switch regions appear to be involved in making contact with effectors and/or regulators of the GTPase activity. These regions can be extremely malleable and have been shown to be involved in the physical association and dissociation of components in the signaling cascade (Sprang 1997).

One of the most important observations concerning G proteins is their regulation by associated proteins (Bokoch and Der 1993). There are two halves to the GTPase cycle: γ -phosphate hydrolysis and $\text{GDP} \rightarrow \text{GTP}$ nucleotide exchange. Both of these steps can be regulated either by inhibition or acceleration of these partial reactions. For example, the Ras protein has an remarkably sluggish intrinsic GTPase activity (Trahey et al. 1987), which can be accelerated at least 10^4 - to 10^5 -fold by a GTPase acti-

vating protein (GAP) (Trahey and McCormick 1987). In addition, there are other regulators of G protein signaling (RGS) that singularly accelerate γ -phosphate hydrolysis, and GDP/GTP exchange factors (GEFs) and guanine dissociation inhibitors (GDIs) that singularly affect nucleotide exchange (Quilliam et al. 1995; Dohlman and Thorner 1997; Tocque et al. 1997). It is interesting to note that highly conserved amino acid domains have been identified within families of these G protein regulators and their ubiquity suggests that similar factors may exist for the A proteins of which the hMSH2-hMSH6 mismatch repair switch would be a prototypical member. The most likely candidate for an adenine nucleotide regulator of the MutS homologs would be the MutL homologs, which would additionally account for the high conservation of MutL domains. Tests of this hypothesis are currently underway.

Biological switches and the second law of thermodynamics

One could argue that the concept of a singular ON or OFF state in a molecular switch might violate the Second Law of Thermodynamics. The Second Law requires that biochemical systems transit one state to the other by a series of microscopically reversible steps. This idea is based in statistical mechanics as it is applied to a system at equilibrium, which must be applied a priori to enzyme catalyzed biological processes. It is easy to visualize the origins of the principle of microscopic reversibility by considering the consequences were it NOT true. For example, if the rate of $\text{A} \rightarrow \text{B}$ were greater than $\text{B} \rightarrow \text{A}$ at equilibrium, each of the rates $\text{B} \rightarrow \text{C}$, $\text{C} \rightarrow \text{D}$, and $\text{D} \rightarrow \text{A}$ would also have to be greater than their reverse rates to prevent buildup of the concentration of any species, which is not permitted at equilibrium. In this case there would be a preferred direction-of-operation of the reaction cycle. Such a spontaneous cycle in a system at equilibrium (i.e., an engine that spontaneously produces work) is not consistent with the drive toward maximum entropy contained in the Second Law.

There is no violation of the Second Law if the transit from an OFF to ON state (or vice versa) occurs reversibly. The molecular basis for this type of microscopic reversibility can be visualized for the hMSH2-hMSH6 and G-protein switches as reversible nucleotide binding as well as intermediate protein conformational changes that occur while transiting the extreme states. It is these conformational transitions that determine interaction with effectors which is ultimately paid for by the hydrolysis of NTP. More significantly, one can affect the equilibrium of each state experimentally by altering the ratio of NDP/NTP in the absence of any hydrolysis (see Fig. 6 in Gradia et al. 1997). It is also important to note that microscopic reversibility has been directly demonstrated for the gated maxi K^+ ion pump, a molecular switch controlled by similar conformational transitions (Song and Magleby 1994). Thus, molecular switches are both reversible and, at equilibrium, clearly preserving a fundamental tenant of thermodynamics.

The marriage of signal transduction and DNA metabolism

The use of controlled molecular switches appears to pervade all aspects of biology. From the standpoint of DNA metabolism, switch controlled processes appear mechanistically sensible. It is well known that the machines which perform replication, recombination, repair and chromosome segregation are very large and composed of multiple subunits (Alberts 1998). Just like the assembly line for an automobile or an airplane, the assembly of DNA metabolic machines must be done precisely and in a specific order to ensure appropriate function. A series of well defined switches could logically control the progression of such an ordered assembly process. Thus, the same type of switch-controlled cascade events that transduce cellular signals may also control DNA metabolic events. The only apparent difference between these switches is the nucleotide that induces the conformational transitions associated with signaling. At the moment the general rule seems to be guanine nucleotides for cellular signaling events and adenine nucleotides for DNA metabolic signaling events. This dogma raises a number of questions: Why purines? Why adenine versus guanine? Is there really generality to these observations? Do these switches signal more than just the assembly of DNA metabolic machines (i.e., are they signals of damage recognition, etc.)? Is there a connection between these DNA metabolic nucleotide-induced molecular switches and cell-cycle checkpoints? Clearly, communication between the fields of DNA repair and signal transduction will provide the breeding ground for appropriate experiments.

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Richard Fishel

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