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DNA Methylation and Mutator Genes in *Escherichia Coli* K-12

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Abstract

Mutator strains of *Escherichia coli* have been used to define mechanisms that account for the high fidelity of chromosome duplication and chromosome stability. Mutant strains defective in post-replicative mismatch repair display a strong mutator phenotype consistent with a role for correction of mismatches arising from replication errors. Inactivation of the gene (*dam*) encoding DNA adenine methyltransferase results in a mutator phenotype consistent with a role for DNA methylation in strand discrimination during mismatch repair. This review gives a personal perspective on the discovery of *dam* mutants in *E. coli* and their relationship to mismatch repair and mutator phenotypes.

Keywords: Alkylating agents; DNA repair; *Escherichia coli;* Mutator; Methylation; Recombination

Introduction

Chromosome replication requires a high degree of fidelity, and studies in *Escherichia coli* K-12 over the last fifty years or so have identified the major mechanisms by which this is achieved. The experimental approach used to solve the fidelity question has relied mainly on the isolation and characterization of mutator strains. A mutator phenotype (Mut) is displayed by mutants that have an increased spontaneous mutation frequency relative to wild type (Mut^+). The underlying assumption is that such bacteria are impaired in systems that normally correct spontaneous replication errors and, in general, this assumption has been correct. It took some time, however, for this assumption to take hold given that the first *E. coli* mutator strain was described in 1954 [1] and systematic screening for mutator strains did not begin until 1970 [2].

In this review I have focused on a group of related mutator strains (and one in particular) that has been the subject of my research for the past few decades. I decided to present a personal view of the developments in this research area in the hope it offers insight into the history of these mutants and will be more entertaining than a formal scientific summary. The latter part of the review is a more conventional summary of mutator genes and their effects, and further details can be found in other reviews [3,4]. Genes discussed in this review are listed with a brief explanation of each (Table 1).

Table 1: *E. coli* genes considered in this article.

Gene	Gene product
dam	DNA adenine methyltransferase
dcm	DNA cytosine methyltransferase
dnaB	Replicative helicase
dnaE	Catalytic alpha-subunit of DNA polymerase III holoenzyme
dnaG	DNA primase
dnaQ	Epsilon-subunit of DNA polymerase III holoenzyme
fpg	Synonym for MutM
hexAB	MutSL homologs
lig	DNA ligase
mutD	Allele of dnaQ resulting in defective proofreading
mutH	Mismatch repair endonuclease
mutL	Mismatch repair protein
mutM	Glycosylase specific for oxidized guanine-cytosine basepairs
mutS	Detects base mispairs to initiate mismatch repair
mutT	Prevents incorporation of oxidized guanine into DNA
mutU	Allele of uvrD
mutY	Glycosylase specific for oxidized guanine-adenine basepairs
polA	DNA polymerase I
polC	Synonym for dnaE
recA	Promotes synapsis of homologous DNA strands
recBCD	Double-strand end-specific exonuclease
ruvA	With RuvB acts as a Holliday junction translocase
ruvB	With RuvA acts as a Holliday junction translocase
ruvC	Holliday junction resolvase
uvrD	Mismatch repair associated helicase

DNA methylation mutants

I was appointed to my first faculty position as an Instructor at Rutgers Medical School (as it was known then) in Piscataway, NJ, in 1971. I had come to join N. Ronald Morris who had been researching DNA methylation in eukaryotes. It seemed worthwhile studying the problem in **E. coli** which, unlike eukaryotes, had both 6-methyladenine (6-meA) and 5-methylcytosine (5-meC) in its DNA. The approach would be a standard one – isolate mutants lacking methylated bases and deduce their functions by examining their properties.

DNA sequence analysis has shown that 5-meC is involved in generating single base changes spontaneously This appears to occur through spontaneous deamina tion of 5-meC to yield thymine. The G/T mismatch upon DNA replication would result in a G-C to A-T base pair change. Deamination of cytosine is not mutagenic, since a specific repair system excises uracil, the deamination product. Evidence for a role for 5-meC residues in genetic recombination has been obtained. One piece of evidence is that dcm mutations suppress the hyper-rec phenotype of arlbacteria. The nature of the interaction between arl and dcm genes and/or products is not clear at present but are under intense investigation. Another role for 5-meC residues might be to alter protein-DNA interactions. That is, a protein may bind differentially to a specific region of DNA depending on the state of DNA methylation. Evidence

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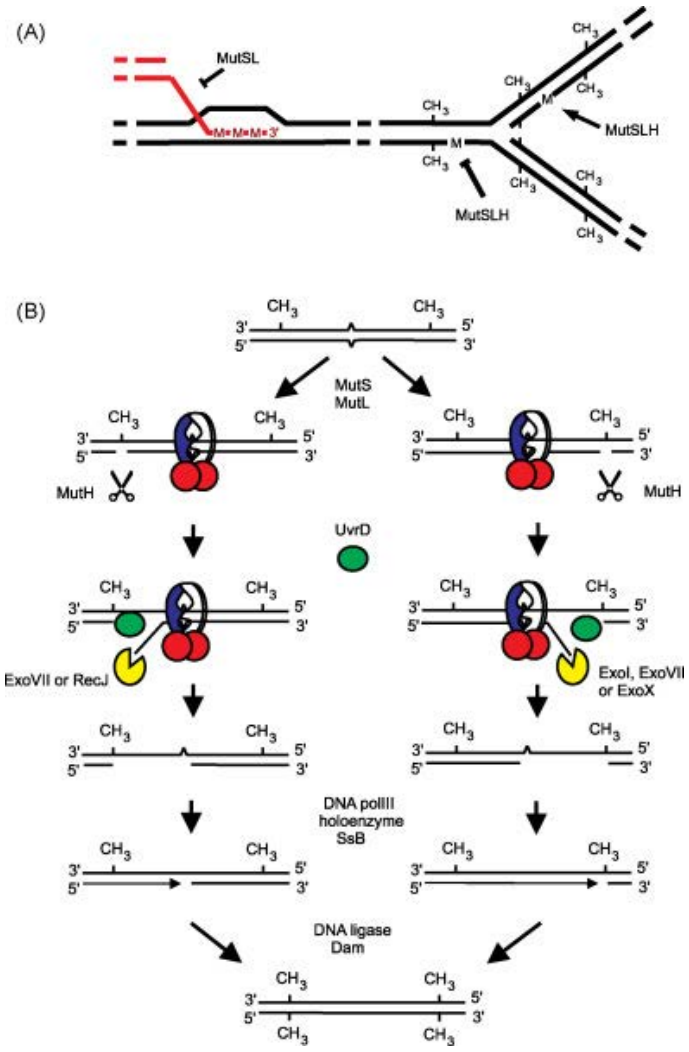

Figure 1: Formation of double-strand breaks in **dam** bacteria. (A) The encounter of a replication fork with a strand discontinuity due to mismatch repair (MMR) results in fork collapse and the formation of a double-stranded end.

for this has recently been obtained. The lexA repressor binds less well to DNA if the binding site does not contain its single 5-meC residue [5]. All dam mutations, except one, map in a single complementation group and are recessive to the wild type allele. In contrast to dcm mutants, dam strains show a variety of phenotypic traits. These include increased spontaneous mutability; increased sensitivity to certain alkylating agents, base analogs and ultra-violet (UV) light; a hyper-rec phenotype; increased induction of lysogenic bacteriophages; inviability of dam- ~-, dam- recB-, dam- recC- and damlexA- double mutants and suppression of some dam phenotypic traits by mutL-, mutS-, sin- and uvrn". These phenotypes a~ot present in dam+ revertants of dam mutants. The pleiotropy of phenotypes suggests that 6-meA and/or the dam methylase have several biological roles in cellular metabolism. A model which accounts for some of the phenotypes of dam- strains has been proposed. It supposes that 6-meA residues determine strand specificity for repair of mismatched bases. That is, the unmethylated strand of a duplex DNA containing a mismatch is subject to excision, whereas the other methylated strand is not. This model can account for the mutability phenotype; the sensitivity to base analogs and the indirect suppression of dam- by mut- mutations. The mutH, and genes have been shown to be involved in mismatch repair (Figure 1).

Acknowledgement:

None

Conflict of Interest:

None

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