MUTATIONAL MECHANISMS IN *MYCOBACTERIUM TUBERCULOSIS*

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Understanding the processes that lead to genomic variation in *Mycobacterium tuberculosis* is of fundamental importance as they underlie the evolution of strains with altered phenotypes. Recent work has shown that the environments encountered by *M. tuberculosis* during an infection are significantly genotoxic, producing lesions that require excision repair for survival of this intracellular pathogen. In many organisms, mechanisms that are induced in response to genotoxic stress play a crucial role in assisting the organism to tolerate the damage. These mechanisms involve the action of specialized DNA polymerases and confer on the organism the ability to adapt genetically to conditions of stress – a property that may be particularly relevant to *M. tuberculosis*. Mycobacteria possess specialized DNA polymerases belonging to both the C- and Y-families. Mycobacterial DnaE2 is the founder member of a new class of C-family polymerases and has been implicated in the evolution of drug resistance in *M. tuberculosis* via a novel tolerance pathway that is under investigation. In contrast, the regulation and function of the Y-family polymerases has remained obscure. To address this question, mutant strains with altered specialized DNA polymerase complements were constructed for use in damage tolerance, long-term survival and mutagenesis studies. The Y-family polymerases were found to be dispensable for growth and survival of mycobacteria *in vitro* and *in vivo*. However, comparative studies of single and multiple mutant strains have begun to uncover non-redundant roles for some of the polymerases in tolerance of specific types of damage and to reveal intriguing relationships between the polymerases and with other proteins that modulate their activities. This work was partly supported by grants from the Howard Hughes Medical Institute, the Wellcome Trust and the NIH (FIC; 5 D43 TW00231).

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