Mechanistic insights into role of DNA polymerase IV in replication and evolution illuminate a novel strategy to combat multidrug resistance

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The increasing appearance of drug-resistant bacteria represents a global health problem of escalating intensity. To develop new antimicrobials, it is imperative to understand- in mechanistic detail- the strategies utilized by bacteria to reduce sensitivity towards therapeutic agents. This knowledge can be used to devise methods to inhibit the function of molecules involved in these processes and thus vastly improve the efficacy of available antibiotics.

In response to stress in the environment, error-prone DNA polymerases (dPols) are upregulated in bacteria and serve to relieve selection pressure imposed by the maladapted environment. Stress-induced-mutagenesis by these dPols is implicated in the onset of drug resistance in pathogenic bacteria. Using DNA polymerase IV (PolIV) from *Escherichia coli* as a model enzyme, my laboratory has discovered the unique attributes in these enzymes that allow them to participate in stress-induced-mutagenesis [*Nuc. Acids Res. (2013) PMID:23525461*]. Also, we have elucidated the mechanism utilized by PolIV to accurately rescue replication stalled at the nitrofurazone (NFZ) derived minor groove DNA adducts and thus neutralize the antimicrobial activity of the NFZ antibiotic [*Structure (2014) PMID:25497730*]. These studies show that PolIV can synthesize DNA accurately past damaged nucleotides and in an error-prone manner on undamaged DNA to aid survival of bacteria. Recently, we have unearthed the structural mechanism utilized by PolIV to incorporate oxidized nucleotides in the genome- an activity that has a deleterious effect on the survival of bacteria. Based on this mechanism, we conducted *in vivo* experiments that ultimately showed that reactive oxygen species do contribute substantially to the antimicrobial activity of bactericidal antibiotics and thus resolved a raging controversy [*Angewandte Chemie* (2015) *PMID:26757158*].

Our studies suggest that perturbation and accentuation of the contributions of PolIV and related orthologs towards survival and lethality may be a viable strategy to develop novel antimicrobials. Overall, our efforts have illuminated a new strategy to combat the escalating global problem of antimicrobial resistance.