Inhibition of Bacterial Mutagenesis through Polyubiquitination: A Solution to Antibiotic Drug Resistance

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Bacterial cells can have DNA damage due to transcriptional error, or through the effect of an antibiotic. The SOS response is a bacterial cell program for coping with DNA damage, in which the cell cycle is arrested, and DNA repair is induced. The repairs have high probability in leading to mutagenesis in the bacteria, which can lead to antibiotic resistance. The RecA protein in bacteria is responsible for regulating the SOS response; therefore, making it a target for inhibition. The ubiquitination system was elected as a means of targeted degradation of the RecA protein in bacteria. Polyubiquitination of misfolded proteins leads to the breaking down of the protein with the aid of proteasomes. Using random forest-predictors, a statistically high likelihood of ubiquitination of the RecA protein in MRSA, TB and other high risk infections was determined. It was hypothesized that ubiquitin-tagging on RecA could be fostered by forcing the protein to misfold. Chaperones are proteins which interact with each other to prevent proteins from misfolding. CHIP (C terminus of HSC70-Interacting Protein) is a biomolecule that inhibits interactions between the chaperones of RecA. Adding CHIP, ubiquitin, and proteasomes into the bacterial system, theoretically leads to the degradation of the RecA protein. This was tested by conducting an assay for monitoring CHIP-mediated ubiquitination, and analysis was conducted using gel electrophoresis, and Western-blotting. The resulting data showed signs of polyubiquitination on the RecA protein, showing high drug potential. Adding an antibody drug conjugate, containing all the components of a CHIP-mediated ubiquitination reaction, to common antibiotics can lead to the inhibition of bacterial mutagenesis, and higher antibiotic drug potency.

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