Evolving Resistance to Hydroxyurea: A Common Chemotherapeutic

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The chemotherapeutic, hydroxyurea (HU), is an antimetabolite drug generally used to treat chronic myelocytic leukemia as well as HIV and sickle cell anemia. Although initial hydroxyurea therapy is often successful, its effectiveness frequently decreases with sustained use due to the development of drug resistance, resulting in further expansion of disease and patient death. Cellular expressions of catalases have been implicated in regulating the response to HU, however the exact mechanism(s) by which cells develop resistance to HU is unclear. This study aimed to develop a bacterial model in order to determine the genes involved in the development of HU resistance. Similar to what has been observed in eukaryotes, expression of bacterial catalases (encoded by katE and katG genes) in Escherichia coli affected cells' HU susceptibility, demonstrating that E. coli is an appropriate model system for studying HU resistance. Following serial rounds of exposure to HU and selection for resistant cells, an evolved strain of E. coli with approximately 100,000-fold increase in survival rate when compared to the parent strain was obtained. It was found that resistance to HU developed in a stepwise progression, suggesting that there are multiple pathways involved in the acquisition of cell resistance to this therapy. Future research will be directed at deep sequencing the genome of this mutant E. coli strain and separately evolving other isolates of HU hyper-resistant E. coli, in order to identify shared mutant genes that can then be screened to determine their role in the development of cell resistance to HU.

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