Characterization of the Role of Catalases in Hydroxyurea Toxicity and Their Potential as Novel Chemotherapeutic Targets

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Hydroxyurea (HU) is a ribonucleotide reductase inhibitor which is used to treat diseases such as HIV, sickle cell disease, and chronic myelogenous leukemia (1). Yet, new evidence suggests that hydroxyurea toxicity may also be dependent upon hydrogen peroxide scavenger proteins, such as catalases (2). Thus, this study aims to elucidate the effects of the scavenging proteins catalase-peroxidase KatE and KatG in cellular damage as a result of hydroxyurea toxicity. To address the role of these proteins, E.coli mutants in each of these genes were constructed and exposed to varying concentrations of hydroxyurea. Both KatE and KatG are shown to have a detrimental effect on cell survival, suggesting that hydroxyurea could act as a catalase-activated pro-drug. In contrast, previous studies of DNA damage induced by hydrogen peroxide have indicated that catalases have no effect in preventing damage, indicating that the cellular pathways for hydroxyurea breakdown differ from that of hydrogen peroxide. Furthermore, the lack of differentiation between KatE or KatG mutant survival in hydroxyurea suggests that the absence of one catalase may deregulate expression of the other. Potential mechanisms for the role of KatE and KatG in cellular damage in the presence of hydroxyurea are discussed.

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