P-12

A COMPLEX PATTERN OF ANTIMUTAGENIC AND POTENTIATING INFLUENCES OF SPERMIDINE AND CYSTEAMINE ON THE GENOTOXICITY OF BLEOMYCIN IN YEAST AND LYMPHOCYTES

George R. Hoffmann, Jennifer L. Fitzpatrick, Gabrielle J. Soron, and Christine J. Willett

Department of Biology, Holy Cross College, Worcester, MA 01610, USA

Antimutagens, including diverse compounds of botanical origin, offer some promise of reducing the risk posed by exposure to mutagens. Caution is warranted, however, as there may sometimes be a delicate balance between antimutagenic effects and potentiating effects of the same compounds. We studied effects of the antimutagens spermidine (SPD) and cysteamine (CSM) on the genetic activity of the radiomimetic cancer chemotherapy drug bleomycin (BLM). BLM is genotoxic in diverse assays. Its activation requires oxygen and an electron source, giving rise to a ferric hydroperoxide that abstracts a hydrogen from the 4'-position of deoxyribose. The resultant free radical is processed into DNA strand breaks. Neither the aminothiol CSM nor the polyamine SPD induces mitotic recombination in yeast or micronuclei in lymphocytes. Both compounds strongly inhibit the induction by BLM of gene conversion at the *trp5* locus in *Saccharomyces*. In contrast, they potentiate the induction of micronuclei in G_0 human lymphocytes. We hypothesize that the difference in responses can be ascribed to oxygen tensions and chromatin configuration. The protective influence of CSM in yeast depends on hypoxia. Under well-oxygenated conditions, CSM potentiates BLM in yeast, as it does in lymphocytes. The potentiating influence of CSM apparently entails its serving as an electron donor for BLM activation or regeneration, while its antimutagenicity is ascribable to the depletion of oxygen needed for BLM activation. In contrast, the effects of SPD most likely occur though DNA binding, which can alter the access of BLM to the 4' position in the minor groove of DNA. Since monoamine oxidase (MAO) is involved in amine metabolism and uses oxygen, we evaluated the effect of the MAO inhibitor pargyline (PG) on the genotoxicity of BLM. PG causes dose-dependent

potentiation of BLM-induced gene conversion in yeast. Supplementary oxygen reverses the potentiating influence of PG, suggesting that PG may potentiate BLM through modulating local oxygen tensions.