


97th AACR Annual Meeting
April 1-5, 2006
Washington, DC

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Presentation Title: Human inter-individual variability in metabolic pathways and genotoxic response to zidovudine
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Poster Board Number: 23
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Patients infected with the human immunodeficiency virus (HIV-1) undergo extensive therapy with antiretroviral nucleoside analog drugs, among which Zidovudine® (AZT) is used the most frequently. The genotoxicity of AZT, a DNA replication chain terminator, has been documented in experimental models, but inter-individual variability in human genotoxic response has not been well studied. Here we used 19 different strains of normal human mammary epithelial cells (NHMECs) cultured from breast tissue obtained at reduction mammoplasty and representing human inter-individual variability. Cells, at passage 6, were exposed to either 0 or 200 µM AZT for 24 hr, and incorporation of AZT into DNA was analyzed by radioimmunoassay using anti-AZT antiserum. Of the 19 cell strains, 7 had no detectable AZT-DNA incorporation, 8 had 6-50 molecules of AZT/10⁶ nucleotides, 2 had 51-100 molecules of AZT/10⁶ nucleotides, and 2 had ≥100 molecules of AZT/10⁶ nucleotides. Exposure to the direct-acting DNA damaging agent bleomycin indicated that these responses were specific for the AZT exposures and not general responses to DNA damage. Further studies were therefore focused on AZT metabolism, and Western blots of all 19 NHMEC strains were performed for thymidine kinase 1 (TK1), the first enzyme phosphorylating AZT on the pathway to DNA incorporation. The 7 NHMEC strains showing no AZT-DNA incorporation had no measurable TK1 before AZT exposure, while 3 of these strains had AZT-inducible TK-1 at 24 hr. Of the 12 strains showing AZT-DNA incorporation, 9 had functional or AZT-inducible TK1. Taken together these data suggest that there may be a metabolic specificity underlying human sensitivity/resistance to AZT. Whereas the patients having high levels of TK1 may sustain more organ genotoxicity as a result of AZT exposure and incorporation, those with lower levels or inducible TK1 still have sufficient enzyme for the antiretroviral properties of the drug, but may be less susceptible to host genotoxic effects.

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