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Copper Isotope Ratios as a Biomarker of Aflatoxin-Induced Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. Aflatoxin B_1 (AFB_1) is a well-known hepatocarcinogen that increases oxidative stress in hepatocytes. In this project, we explore the isotopic response of stable Cu ($^{65}Cu/^{63}Cu$) to oxidative stress and further aim to establish a sensitive tool for the early detection of aflatoxin-induced HCC.

We analyzed liver and serum samples from rats ranging from 43 to 90 weeks old which were part of a lifetime cancer bioassay. The sample set included two groups; group one (AFB_1) was orally dosed with AFB_1 and a vehicle solution. Group two (AFB_1 + CDDO-Im) was dosed with AFB_1 and a potent Nrf2 activator, CDDO-Im, as a chemoprotective agent. A high percentage of rats in the AFB_1 group (22/23 rats) developed HCCs. CDDO-Im provided complete protection (20/20 rats) against liver cancer.

Hepatic tissues (tumor and non-tumor) and sera were digested, and Cu was purified using AG-MP1 anion exchange resin. Cu isotope ratios of all samples were measured by MC-ICP-MS in triplicate, and reproducibility was additionally verified with a secondary internal standard (ESPI, $\delta^{65}Cu_{VNIST976}$ = +0.17 ± 0.01‰ (2SE, n = 72)). All standards and samples were doped with a certified $^{69}Ga/^{71}Ga$ standard (NIST SRM 994), an internal standard to correct for mass bias.

Comparison of $\delta^{65}Cu$ values between nontumorous hepatic tissue samples from the AFB_1 + CDDO-Im group (n = 10, mean $\delta^{65}Cu_{VNIST976}$ = -0.48‰) and tumorous tissue samples from the AFB_1 group (n = 16, mean $\delta^{65}Cu_{VNIST976}$ = -0.32‰) showed a relative enrichment of ^{65}Cu in tumorous tissue with a statistically significant difference (p = 0.016). Work is ongoing to analyze $\delta^{65}Cu$ values of sera, and those results will be presented at the conference. Our results show the preferential transport/accumulation of ^{65}Cu in tumorous tissue after AFB_1 exposure, demonstrating a novel application of copper stable isotope analysis to a chemically induced hepatocarcinogenesis model and highlighting its potential as an early, mechanism-linked biomarker of carcinogen-driven HCC.