Hypoxia induces copper stable isotope fractionation in hepatocellular carcinoma, in a HIF-independent manner

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Recently, altered trace metal isotopic compositions have been documented for different human diseases, including cancer. This opens up the possibility that metal isotope analysis be used for diagnosis and prognosis. However, the reasons behind such isotopic signatures remain elusive and in order to clarify them, experimental approaches are needed (1, 2).

Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer and interestingly, copper in HCC tumours is enriched in the heavy isotope, as compared to the surrounding tissue (3). The unrestrained proliferation of tumour cells leads to tumour hypoxia, which in turn promotes cancer aggressiveness. We used human cell biology methodologies, in order to test the role of hypoxia in the copper isotope fractionation observed in HCC. Strikingly, we found that hypoxia causes heavy copper enrichment in several human cell lines. Moreover, we demonstrate that this effect of hypoxia is pH, HIF-1 and -2 independent. Our data identify a previously unrecognized cellular process associated with hypoxia, and suggest that in-vivo tumour hypoxia leads to copper isotope fractionation in HCC and other solid cancers.

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