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Widespread 8-oxoguanine modifications of miRNA seeds differentially regulate redox-dependent liver cancer development

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Oxidative stress contributes to tumorigenesis by altering gene expression. One accompanying modification, 8-oxoguanine (o^8G) can change RNA–RNA interactions via o^8G•A base pairing, but its regulatory roles remain elusive. Here, on the basis of o^8G-induced guanine-to-thymine (o^8G > T) variations featured in sequencing, we discovered widespread position-specific o^8Gs in tumor microRNAs, preferentially oxidized towards 5′ end seed regions (positions 2–8) with clustered sequence patterns and clinically associated with patients in liver hepatocellular carcinoma. We validated that o^8G at position 3 of miR-122 ($3o^8G$-miR-124) and $4o^8G$-let-7 promote malignancy of liver hepatocellular carcinoma by redirecting the target transcriptome to oncogenic regulatory pathways. Stepwise oxidation from tumor-promoting $3o^8G$-miR-122 to tumor-suppressing $2,3o^8G$-miR-122 occurs and its specific modulation in mouse liver effectively attenuates diethylnitrosamine-induced hepatocarcinogenesis. These findings provide resources and insights into epitranscriptional o^8G regulation of microRNA functions, reprogrammed by redox changes, implicating its control for liver cancer treatment.