

JOINT EVENT ON

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Chronic circadian dysfunction is an independent risk factor of cancer**Loning Fu**

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Lifestyle change-induced physiological dysfunction and non-inherited genetic mutations drive increased cancer risk among general populations. One of the major lifestyle changes since industrial revolution is chronic circadian disruption, which has reached epidemic levels in modern societies. Mounting evidence accumulated from human epidemiological studies has established a strong link between chronic circadian disruption and increased cancer risk. Circadian homeostasis is maintained by an endogenous circadian clock operated by genes in all species studied. Ablation of the core circadian genes in mice increases the risk of both tumorigenesis and progression. However, circadian gene mutations are not associated with population-wide chronic circadian disruption or the majority of human cancers. To define the mechanism of circadian dysfunction-induced cancer risk, we established a chronically jet-lagged wild-type (WT) mouse model following a human night-shift working schedule. We found that chronic circadian dysfunction increases the risk of obesity-related metabolic syndrome and cancers in WT mice as observed in human night-shift workers, with non-alcoholic fatty liver disease (NAFLD)-related hepatocellular carcinoma (HCC) as one of the most frequently observed tumors. We found that chronic jet lag induces spontaneous HCC in mice following a mechanism very similar to that observed in obese humans, which initiates with non-alcoholic fatty liver disease (NAFLD) that progresses to steato hepatitis and fibrosis before HCC detection. We demonstrate that chronic jet-lag induced neuroendocrine dysfunction is sufficient to induce genome-wide gene deregulation, peripheral clock disruption, and global liver metabolic dysfunction independent of somatic gene mutations and changes in other life-style factors. Our extensive molecular, metabolomics, pathological, and genetic analyses defined nuclear receptor-controlled cholesterol/bile acid and xenobiotic metabolism, especially those controlled by the bile acid receptor FXR and xenobiotic receptor CAR, as the top deregulated pathways that promote spontaneous hepatocarcinogenesis. Together, our studies demonstrate that tumour suppression is a clock-controlled physiological function, and that chronic circadian dysfunction is an independent risk factor of HCC. Our findings also suggest that restoration of the homeostasis of bile acid metabolism and signalling are promising complementary strategies for prevention of NAFLD-induced HCC in humans, which has displayed an alarming rate of increases in recent years coupled with the prevalence of obesity and chronic circadian disruption.

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