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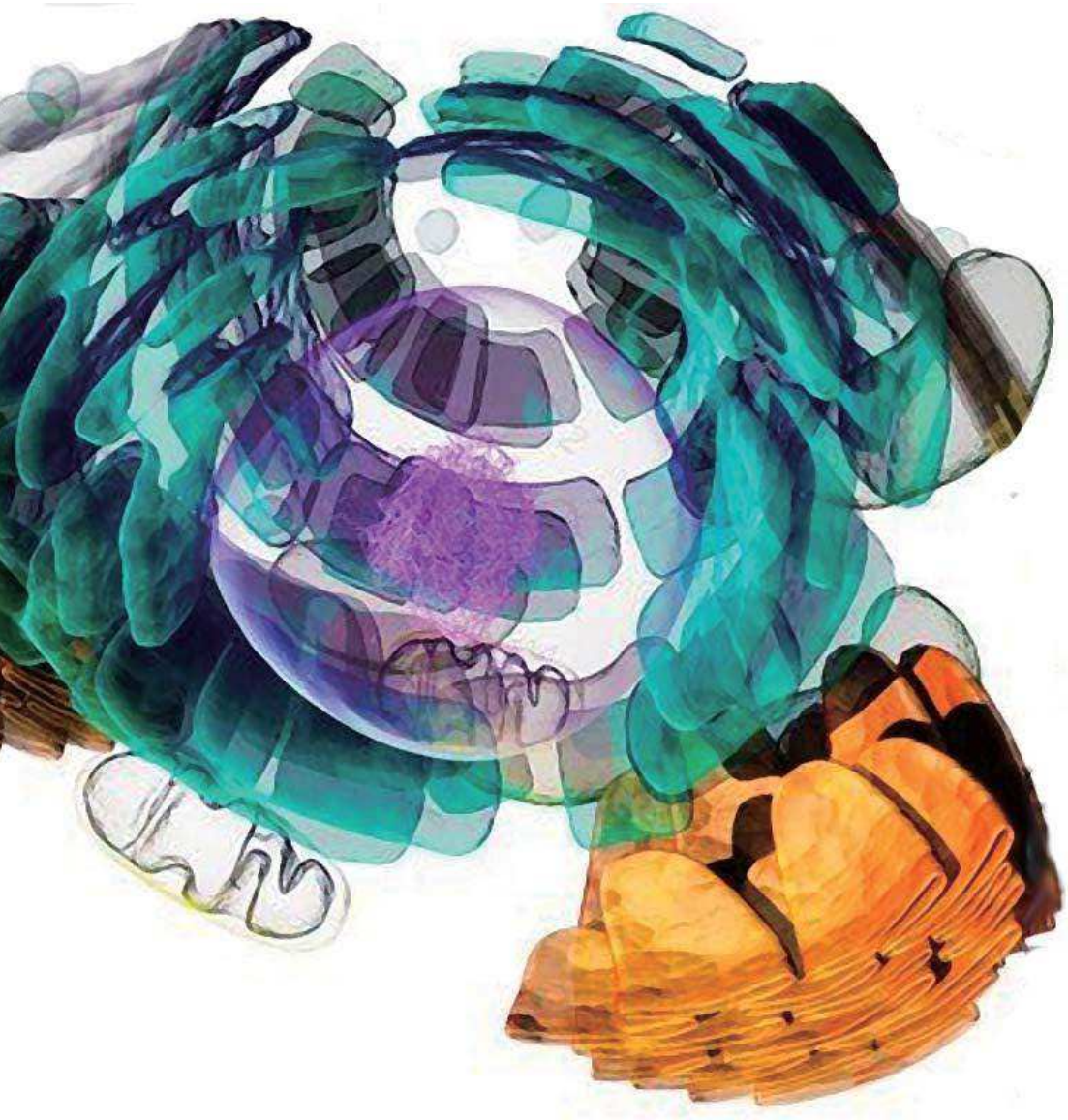

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Molecular Basis of Circadian Desynchrony in Cardiometabolic Disease

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Abstract:

The circadian system is a key integrator of behavior and metabolism that synchronizes physiological process to anticipate and respond to recurrent daily changes in the environment. Studies from our laboratory have shown that, in addition to disruption in circadian activity rhythm and sleep-related pathologies, perturbation of normal circadian gene function leads to diet-induced obesity and cardiometabolic syndrome. Conversely, high fat diet (HFD) disrupts sleep, feeding, and locomotor activity rhythms. These observations raise interest in uncovering signaling mechanisms intersecting nutrient flux and dietary lipid composition to circadian homeostasis, at both the behavioral and gene regulatory levels. Here, we show that mice fed a diet high in saturated fat display increased activity during the normal rest (light) period in contrast to mice provided control diet (i.e. regular chow). In addition, saturated and unsaturated fat diets show opposite effects on circadian activity rhythm: HFD containing mainly saturated fatty acid (SFD) lengthened circadian period whereas an isocaloric diet containing unsaturated fatty acids (UFD) shortened the period. The effects of each diet were examined at the level of isolated live cultures of suprachiasmatic nuclei (SCN) in genetic reporter mouse, mPer2Luc, to compare the effects of saturated versus unsaturated fat master pacemaker neurons. Remarkably, the overt behavioral effects of HFD on locomotor activity were recapitulated in live-cell cultures of SCN from mPer2Luc mice. These observations delineate a relationship between dietary fatty acid composition per se on behavioral and molecular circadian rhythms in mice. Genetic and nutritional manipulations provide a new entry point to probe the reciprocal relationship between obesogenic diet and circadian disruption.