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Circadian Metabolic Oscillations in the Epidermis Stem Cells by Fluorescence Lifetime Microscopy of NADH in Vivo

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There is a lack of non-invasive methods to monitor circadian metabolic oscillations of single cells in their native environment. Here we implement a label-free method using NADH as an intrinsic biomarker and the Phasor approach to Fluorescence Lifetime microscopy to measure the metabolic optical fingerprint of single cells during the day-night cycle. For the first time we detect in vivo metabolic circadian oscillations within the stem cells of the epidermis layer. We observe higher ratios of free/bound NADH, i.e. NADH/NAD^+ , in the night with respect to the day. This difference indicates a glycolytic phenotype associated with high proliferation during the night and an oxidative phosphorylation phenotype associated with low proliferation during the day. We demonstrate that cell-to cell metabolic heterogeneity correlates with circadian phase as measured within the basal epidermal layer by Per1-Venus reporter assay. Finally, we show that NADH metabolic oscillations are Bmal1 dependent.

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