MEDICAL THERAPIES AND PHARMACOLOGY

CIRCADIAN RHYTHMS IN HUMAN DERMIS, EPIDERMIS, AND SEBACEOUS GLANDS

Gang Wu [(1)] - Marc D Ruben [(1)] - Lauren J Francey [(1)] - David F Smith [(2)] - Joseph D Sherrill [(3)] - John E Oblong [(4)] - Kevin J Mills [(3)] - John B Hogenesch [(1)]

Cincinnati Children's Hospital Medical Center, Center For Chronobiology, Department Of Pediatrics, Cincinnati, United States [(1)] - Cincinnati Children's Hospital Medical Center, Divisions Of Pediatric Otolaryngology And Pulmonary And Sleep Medicine, Cincinnati, United States [(2)] - The Procter & Gamble Company, Biosciences Division, Mason, United States [(3)] - The Procter & Gamble Company, Beauty Technology Division, Mason, United States [(4)]

Introduction: Skin is the largest human organ and has important barrier, regulatory, and sensory functions.

Objective and Materials & Methods: We investigated the role of the circadian clock in the transcriptional regulation of human dermis, epidermis, and sebaceous glands from hundreds of volunteers using CYCLOPS, a recently described algorithm to determine sample phase from unordered genome scale data. We also evaluated genome scale molecular rhythms in epidermis and dermis. We used Phase Set Enrichment Analysis (PSEA) to evaluate clock regulation at the pathway level in both skin layers, with similar results.

Results: We found that the epidermis had the strongest signature of clock function, followed closely by the dermis, while the sebaceous gland had a weak signature of circadian function. This order was independent from the anatomic location of sample collection, as similar signatures were seen in sun exposed forearm and cheek and the presumably sun-deprived buttocks. Sample phases from each volunteer were consistent between dermis and epidermis. The epidermis had higher amplitude circadian rhythms in the core clock genes BMAL1, NR1D2, PER2, PER3, and NFIL3. Hundreds of clock-regulated genes were found in each layer in two roughly equivalent bursts at dawn and dusk. Two pathways, lipid metabolism and the immune system, were clock regulated in both layers and shared similar phases.

Conclusions: In sum, the epidermal layer of human skin has the strongest signature of clock function, suggesting its utility as a source of human biomarkers of circadian phase. This signature was invariant across body regions, suggesting broad flexibility in where samples can be collected. We are further delineating the orchestrated temporal programs of gene

expression in skin and how this information can be leveraged to improve human health and appearance.