Metabolomics Highlights: The Importance of Circadian Rhythm in Skin

New insights on the critical role of maintaining the natural rhythm of skin protection and repair.

BY NADINE PERNODET, PHD AND PAOLO SASSONE-CORSI, PHD

>> The study of "-omics" continues to impact the medical research and skincare landscapes by providing greater understanding of how the body can connect molecular pathways and by defining biological networks to improve the basic understanding of how skin works.

To expand upon the evolving study of "-omics," The Estée Lauder Companies (ELC) initiated a first-of-its-kind study examining the metabolome of facial skin from youthful and mature individuals in the morning and evening. This study is the first to show that the natural youthful metabolomic rhythm in skin is altered with age, leading to lower repair and more skin damage. This study supports ELC's decade-long commitment to skin circadian rhythm research.

Metabolomics is the study of metabolites, the substrates and outputs of cellular processes that inform what we know about the functions of biological systems like the skin. Thus, metabolites reflect the environment, lifestyle, and the microbiome, informing on every biological process occurring in skin and work to connect molecular pathways in our body.[1] Groundbreaking research investigating the interconnectivity of these pathways, or skin bio-networks, highlights ways in which we can leverage these connections to affect skin natural activities and improve its appearance.

Metabolomics offers a more direct link to phenotype than any of the other "-omics" platforms because it is highly dynamic and precise. Recognizing the effects of environmental factors, such as sunlight and pollution, is crucial when it comes to understanding skin biology and skincare. Once metabolomic networks have been established to define phenotypes, the patterns allow us to identify an individual's metabolomic profile, or their own unique "metabolomic fingerprint." This "fingerprint" is a holistic snapshot of an individual's skin condition at a specific point in time, which can be used to suggest targeted or customized treatments.

SKIN FINGERPRINT

By using metabolomics to assess circadian rhythm dynamics from the human skin surface with non-invasive D-squame collection methods, scientists are able to temporally define the skin metabolome. Advancements in metabolite measurement, using in vivo sampling of a specific

Metabolites reflect the environment, lifestyle, and the microbiome, informing on every biological process occurring in skin, and work to connect molecular pathways in our body. Research investigating the interconnectivity of these pathways, or skin bio-networks, highlights ways in which we can leverage these connections to affect skin natural activities and improve its appearance. New research highlights how metabolomics enables us to establish skin functions by non-invasively examining the skin surface, ultimately providing in vivo diagnostics of skin. This study establishes the foundation of the skin circadian metabolome with the first in vivo study showing most metabolites in young skin follow a natural rhythm of protection and repair.

the**bottom**line

> "Proper circadian rhythms are essential to the appearance of skin, as your skin performs very different functions during the day versus at night. When healthy and young, skin follows a very strong circadian rhythm with timed cellular functions. It supports and maximizes skin protection during daytime and engages in repair and recovery during nighttime."

population, provide the ability to view complex patterns as a network that yields an overview of skin's current state. Metabolite profiles show cycles of protection and repair, which therefore provide insights into how to maximize the repair processes in damaged skin.[1]

The ability to view these complex patterns as a network, or "skin fingerprint" has been made possible in the last decade by new biological techniques that analyze massive data sets in order to elucidate how multiple pathways are interconnected and how they influence one another.

IMPORTANT ROLE OF CIRCADIAN CLOCKS

The circadian clock guides cellular functions during protection and repair cycles, creating an oscillation of cell activity that repeat every day, the so-called circadian rhythm. Specific metabolic pathways are reflective of the current status of circadian clocks. This means metabolism and circadian clocks are inextricably linked. Information gained from these studies resides at an important interface between skin care and technology. Further, these techniques can be used as surrogate diagnostic and predictive biomarkers to define health or pathology.

Recent studies from the Center for Epigenetics and Metabolism at the University of California, Irvine, illustrated that circadian clocks can be rewired by factors such as sleep deprivation, diet, and exercise. In addition, ubiquitous exposures to blue light from devices including the computer, television, or cellphone light just before bed can alter internal clocks. These daily interferences cause our circadian systems to get desynchronized, and in turn, can lead to depression, allergies, premature aging, cancer, and other health problems—as well as impacts on skin aging.

Proper circadian rhythms are essential to the appearance of skin, as your skin performs very different functions during the day versus at night. When healthy and young, skin follows a very strong circadian rhythm with timed cellular functions. It supports and maximizes skin protection during daytime and engages in repair and recovery during nighttime. ELC research in skin circadian rhythm has established that metabolomics is a critical diagnostic tool for skin science and supports the understanding of circadian rhythm and highlights the importance of time, both in the proper orchestration of daily timed functions and of the changes due to time in terms of years.[1]

DECADE LONG SKIN CIRCADIAN RESEARCH

Recognizing the connection between skin and circadian clocks, the Estée Lauder Companies, pursued research to expand this area of understanding for skin. Researchers aimed to identify specific biomarkers that indicate which skin phenotype a population exhibit in order to identify how age and treatment may influence the protection and repair mechanisms controlled by circadian rhythm.

By identifying biochemical changes in the facial skin, this research reveals, for the first time, that the skin metabolome follows a circadian rhythm in young women—a rhythm that ensures the skin is undergoing optimal protection and repair at the correct time. Importantly, this research also found that a loss of circadian rhythm a common feature of mature skin—can lead to skin damage.

Researchers used non-invasive sampling strips to collect samples from the facial skin surface of youthful and mature Caucasian women, both in the morning and at night. Metabolites were isolated from these samples and subjected to untargeted metabolic profiling via a multi-method LC/MS/

MS platform. Three hundred of the identified metabolites were shown to be relevant to the look of skin. Of these, two hundred and twenty metabolites were found to change with age, translating a change in the rhythm of protection and repair mechanisms. The study found 186 of the metabolites follow a distinct circadian rhythm in young skin, but only 44 metabolites retain their natural rhythm in mature skin. Of the 186 metabolites that follow a rhythm in youthful skin, ELC scientists analyzed trends for young, mature, and mature with a treatment containing a PER1 activator to support skin's natural circadian rhythm. The metabolites were classified into categories: oxidative damage, inflammation, protein breakdown, and barrier integrity/moisturization.

What is Metabolomics?

According to the European Bioinformatics Institute (EMBL-EBI), Metabolomics is the large-scale study of small molecules, commonly known as metabolites, within cells, biofluids, tissues, or organisms. Collectively, these small molecules and their interactions within a biological system are known as the metabolome.

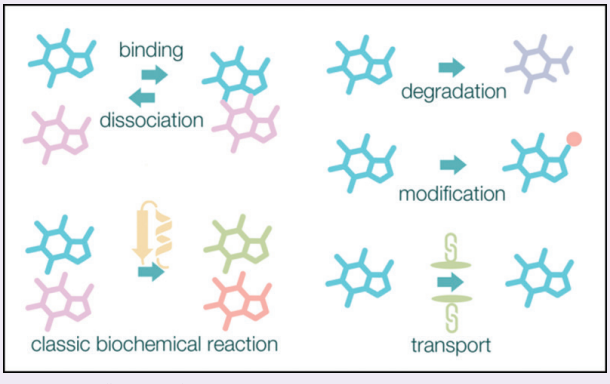

Figure. The main different types of metabolic reactions that take place in a cell. These are shown as they are represented in the EMBL-EMI database.
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The Institute notes that the non-invasive nature of metabolomics and its close link to the phenotype make it an ideal tool for the pharmaceutical, preventive healthcare, and agricultural industries, among others. Biomarker discovery and drug safety screens are two examples where metabolomics has already enabled informed decision making. In the future, with the availablity of personalised metabolomics, we will potentially be able to track the trends of our own metabolome for personalised drugs and improved treatment strategies. Personalised treatment is likely to be more effective than our current medical population-based approaches.

Oxidation

In young skin, a clear natural rhythm is observed. Oxidative damage—the imbalance between free radicals and antioxidants in the body—is low in the morning and increases over the course of the day. Each night, healthy young skin efficiently repairs and removes the accumulated damage, and the cycle repeats each day. However, in mature skin, there is a very high increase of oxidative damage accompanied by an inversed circadian rhythm, showing a poor repair efficiency.

Inflammation

In young skin, inflammation is lower in the morning and increases over time with an increase in skin damage. In mature skin, inflammation is much higher, experiencing an almost constant state of inflammation, which translates to an increase in damage and a loss of repair abilities.

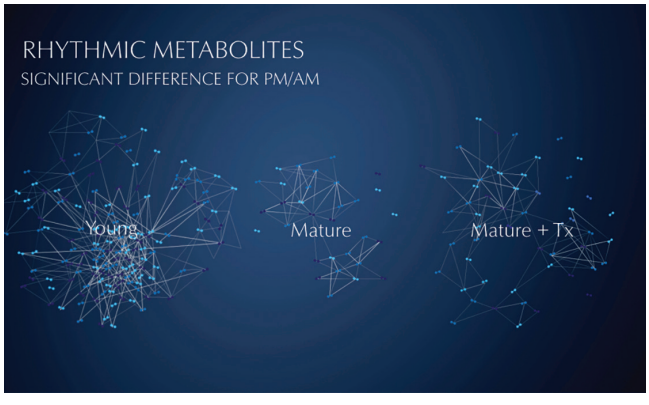
Protein Damage

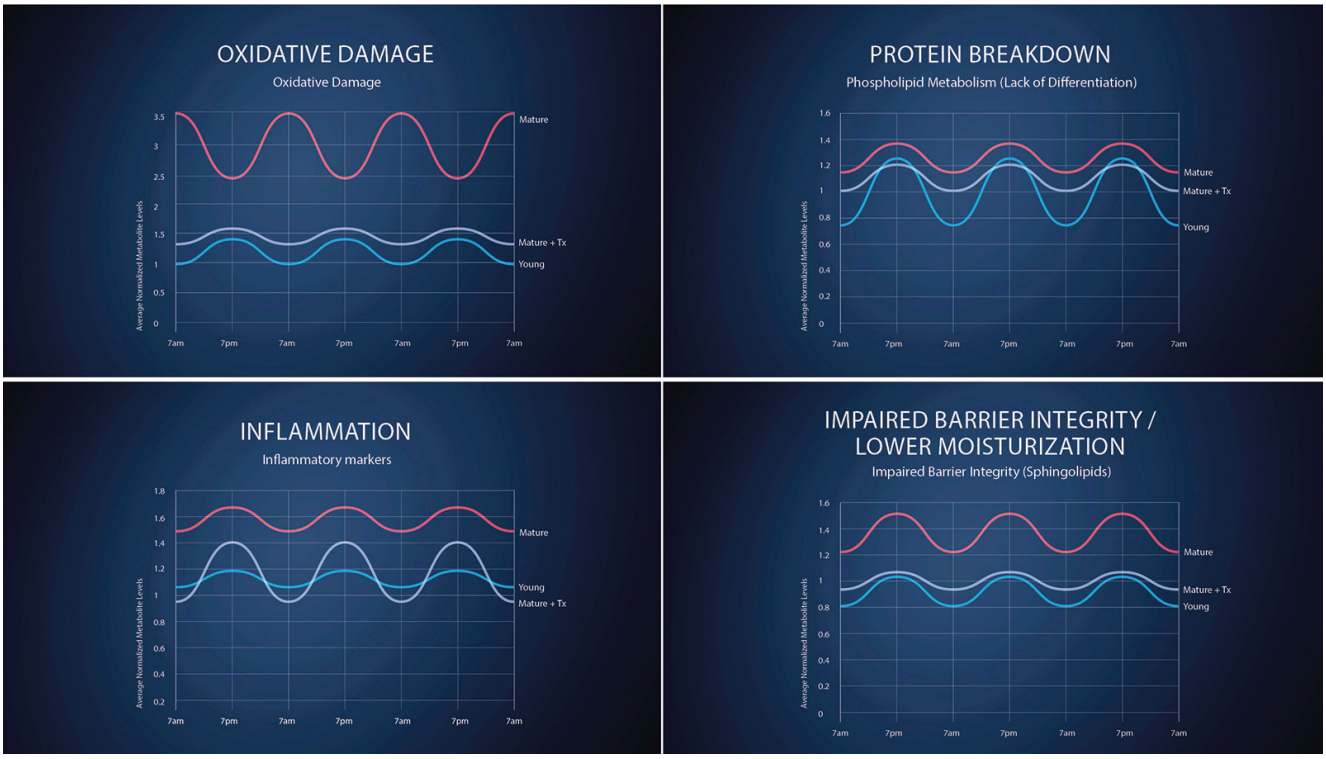
In young skin, protein damage increases over the course of the day and is repaired overnight. However, in mature skin, protein damage is much higher than in young skin, and repair is less effective, which leads to an accumulation of protein damage (i.e., loss of skin mechanical properties).

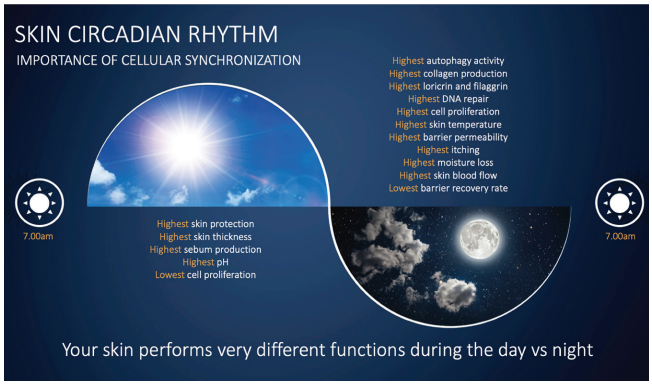
Barrier Integrity

In young skin, barrier integrity is highest in the morning, reflecting the importance of protection during the day. Metabolites associated with a lack of differentiation and lower moisturization are at their lowest level in the morning, indicating that differentiation has occurred overnight to build the strongest barrier. While this rhythm is maintained in mature skin, the levels are much higher, indicating that barrier integrity is impaired.[2]

In summary, this research highlights how metabolomics enables us to establish skin functions by non-invasively examining the skin surface, ultimately providing in vivo







diagnostics of skin. This study establishes the foundation of the skin circadian metabolome with the first in vivo study showing most metabolites in young skin follow a natural rhythm of protection and repair. This is the first study to demonstrate the ability to re-establish levels and rhythm of key metabolites in mature skin with treatment. In addition, we have confirmed a natural rhythm of skin, focusing on protection in the daytime and switching at night to focus on repair through real-time metabolomic analysis. Based on this research, we have established that a technology designed to direct timing of specific cellular functions can shift key metabolites and help re-establish skin's ideal rhythm.

WHAT THIS MEANS FOR THE FUTURE OF SKIN SCIENCE

In the future, metabolomics may allow skincare professionals to provide customized treatment options based on individual skin metabolomes. This research will help the industry further define metabolic profiles associated with other skin conditions, including acne, sensitive skin, and dry skin and will contribute to the body of literature investigating how various skin bionetworks affect skin's appearance. ■

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