

# Calcium ions and healthy skin

Key process gives insight for future skin therapies

Our skin is the first line of defence from external harm and a central part of the thermoregulatory system. Dr Richard Evans and Dr Andrew Mayes of Unilever Research & Development in the UK, alongside a team of collaborators from the University of Liverpool, UK, present mounting evidence regarding the essential role of store-operated calcium entry (SOCE) for normal skin function. In a recent review article, members of the team describe the underlying mechanisms and chief proteins involved in detecting calcium levels and in regulating their influx and efflux in skin cells. Insight into these mechanisms gives scientists the power of knowledge to design treatments for associated skin conditions.



The primary function of our skin is to shield our tissues from the external environment. This organ, the largest in our body, protects us from physical harm and environmental threats such as ultraviolet (UV) light and dehydration. It also helps regulate our body temperature by sweating, which helps cool our skin. Emerging research suggests that a process known as 'store-operated calcium entry (SOCE)' underpins the normal physiological functioning of a range of skin cells.

SOCE is the process where stocks of calcium within cells become depleted, triggering the entry of calcium ions

## Emerging research suggests that a process known as 'store-operated calcium entry (SOCE)' underpins normal physiological functioning of skin cells.

into the cell from the outside, and in turn, inducing the cells to respond in some way. In their latest review paper published in the journal *Frontiers in Physiology*, Dr Richard Evans of Unilever Research & Development and collaborators, Professor Caroline Dart and Dr Declan Manning at the University of Liverpool, UK, summarise the recent evidence for the vital role played by SOCE and the key proteins stromal interaction molecule 1 (STIM1) and Orai1 in the maintenance of healthy skin.

Three cell types which are prevalent in skin are keratinocytes, melanocytes, and eccrine sweat gland secretory coil cells (see Figure 1 for details on their location within the skin structure). The epidermis

is the outer layer of the skin and consists mainly of keratinocytes. These cells need to differentiate in order to form the toughened or 'cornified' layer and provide protection from mechanical injury. Keratinocyte differentiation is also required for normal skin physiology and for maintaining healthy, hydrated skin.

### SOCE: A CRITICAL FACTOR IN DIFFERENTIATION AND SKIN CONDITION

When keratinocytes in the basal or deeper layer of the epidermis proliferate or multiply in number, they are immature and unable to fulfil their function. To do so, they must go through the process

of differentiation as they are 'pushed up' towards the outermost layer of the skin. In its simplest form, keratinocyte differentiation is the maturing of keratinocytes marked by changes in their characteristics, including shape and function. The process, however, is far more complex than that and involves a set of changes at the molecular and organelle level in cells.

Skin cell differentiation is driven by higher calcium concentrations in the outer layers, specifically the stratum granulosum, compared to the deeper layers (as shown in Figure 1). The calcium-sensing receptor (CaSR) detects this calcium gradient. It activates the messenger, inositol trisphosphate (IP<sub>3</sub>),

which depletes calcium stocks and, in doing so, ultimately triggers SOCE (see Figure 2, which explains the process in each cell type mentioned) and cell differentiation by altering the expression (or level) of genes and proteins.

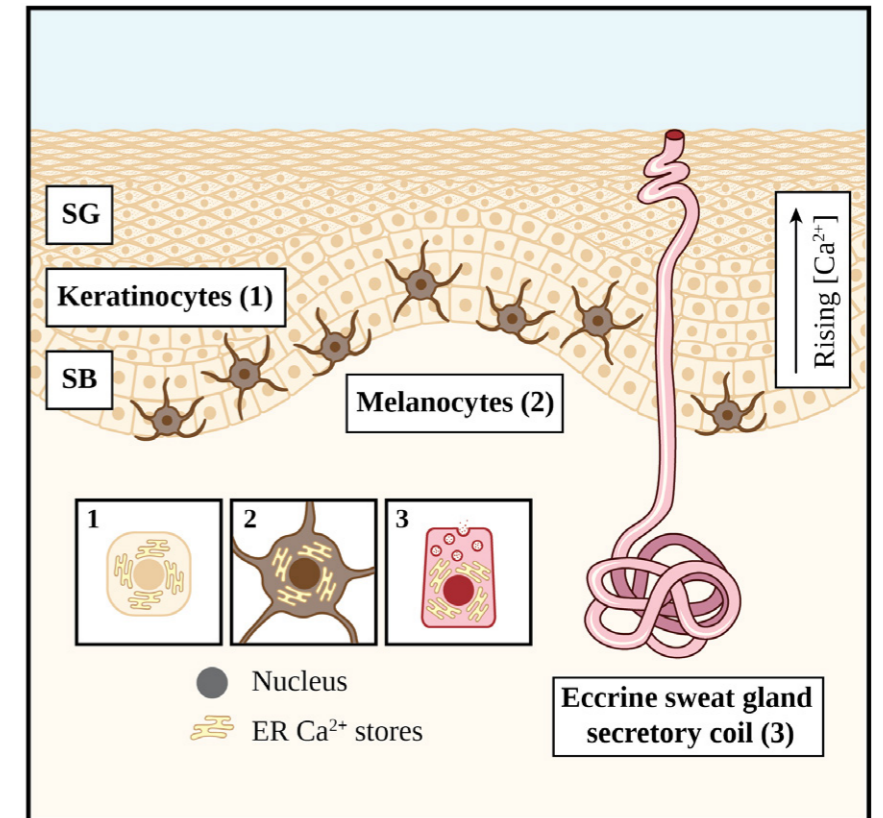
The importance of STIM proteins and Orai channels to SOCE and epidermal functioning has also been demonstrated by others in mice where reduction of STIM1 and Orai1 protein expression decreases keratin 1 expression, a protein essential for skin integrity. Furthermore, mice without Orai1 have thinner skin, emphasising the importance of Orai1 for normal skin structure and function.

If SOCE is dysfunctional, then calcium stores are not restocked. In such cases, this would impact the skin cells that help form the epidermal calcium gradient and drive keratinocyte differentiation. Such dysfunction could lead to dry or sensitive skin, and in extreme cases even more severe skin conditions such as dermatitis (skin irritation), anhidrotic ectodermal dysplasia (a genetic disorder affecting the skin, sweat glands, hair, and teeth), and hyperhidrosis (excessive sweating; see later) which are all known to be linked to abnormal SOCE and its proteins.

While Orai channels are thought to be the fundamental drivers of keratinocyte differentiation, evidence is emerging that they are not the only channels regulating calcium influx in these cells. It is now becoming increasingly evident that transient receptor potential canonical (TRPC) proteins are likely to play a role in SOCE. In their latest work, also published in *Frontiers in Physiology*, Manning, Dart and Evans use high-resolution microscopy of keratinocytes to explore the potential mechanisms underlying TRPC1 channel activation.

### MELANIN AND SKIN PIGMENTATION

When exposed to sunlight, melanocytes produce the skin pigment melanin to protect the keratinocytes from damage which could be induced by the ultraviolet (UV) radiation in sunlight. Melanin production leads to darkening or 'tanning' of the skin. The processes and functions of melanocytes are known to be regulated by melanocyte-inducing transcription factor (MITF), which controls a number of associated genes. Upregulation of



SG = Stratum corneum; SB = Stratum basale; ER = Endoplasmic Reticulum

Figure 1. Cross-section of the skin showing the main skin cell types.

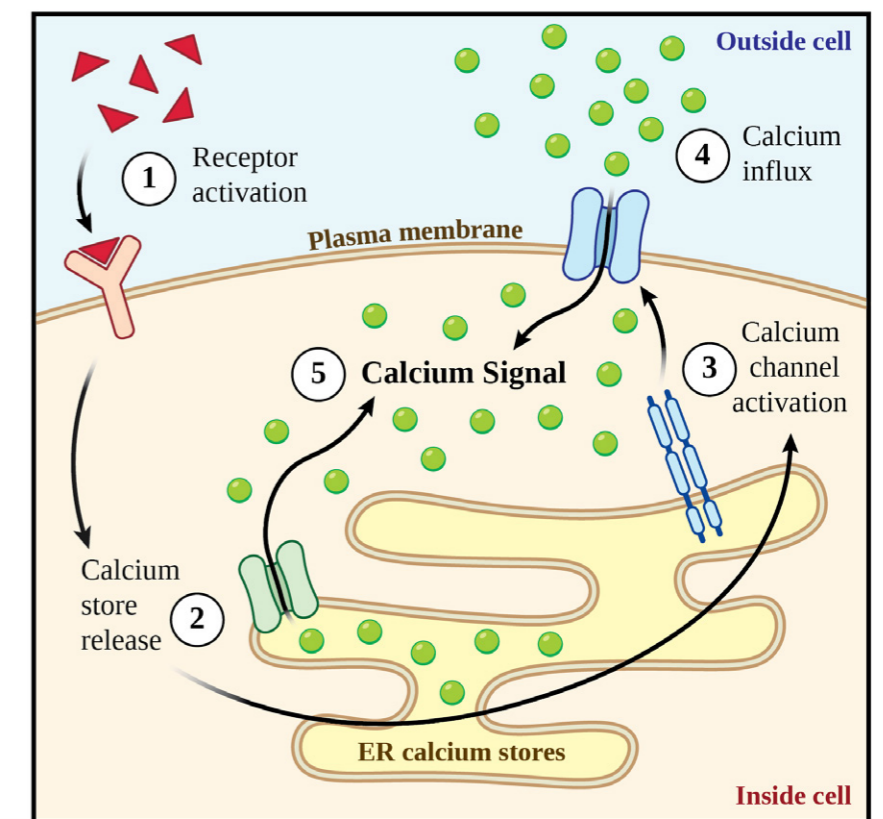


Figure 2. Store-operated calcium entry in the main skin cell types.



SOCE dysfunction may lead to dry or sensitive skin, and in extreme cases, even skin conditions.

MITF causes skin pigmentation and can lead to either adaptive melanogenesis (or 'adaptive tanning'), or to standard baseline melanogenesis.

Alpha-Melanocyte Stimulation Hormone ( $\alpha$ -MSH) activates the melanocortin one receptor (MC1R) in a well-established pathway central to melanin production. In fact, mutations in MC1R genes can be found in fair-skinned, red-haired people with low melanin levels. Recent findings point towards a role played by calcium-dependent proteins such as STIM1 in this pathway, with experiments demonstrating that reducing STIM1 decreases melanin production.

Other studies suggest that SOCE and Orai1 have a part to play in adaptive melanogenesis, building evidence for the role of SOCE in regulating the process of skin darkening and its final colour. The role of SOCE may be particularly relevant to body areas prone

to increases in skin pigmentation. These areas include the underarm (or axilla) where irritation from hair shaving or plucking, and the use of harsh soaps and 'enthusiastic' towel drying can lead to some skin darkening over time.

#### HOT AND SWEATY: SOCE IN THERMOREGULATION

The eccrine gland is the 'sweat gland' that produces sweat to cool the skin and the body. This process begins with the neurotransmitter acetylcholine stimulating

### A deeper understanding of SOCE as a fundamental process underlying normal physiological function of skin opens avenues for further research and therapy development.

the release of calcium from intracellular stores, triggering calcium influx from external sources by SOCE (see Figure 2) in the secretory coil cells of the eccrine gland. The second step in the process of sweating involves the movement of

chloride ions across the secretory coil cells into the glandular lumen. Cultured cell and human studies again implicate STIM1 and Orai1 as the key proteins in the SOCE process required for sweat secretion. The strongest evidence for their role in the process is that deleting expression of these proteins (by gene knockdown) in model systems results in impairment of the calcium signal, and by implication sweating. Conversely, eccrine coil cells from people with hyperhidrosis (excessive sweating) reveal overexpression of STIM1, an exaggerated calcium influx and SOCE response, and consequently enhanced sweating.

A deeper understanding of SOCE as a fundamental process underlying normal physiological function of the skin opens avenues for both further research and therapy development. Evans and collaborators have summarised existing data and provided new insights in their recent publications which emphasise just how pivotal the role of calcium regulation and SOCE is for skin health. They have also identified gaps in our knowledge,

highlighting focus areas for future work. Considering SOCE's significant role across a range of skin functions, improved understanding of the underlying mechanisms will

certainly provide opportunities for the development of better treatments for a diverse range of skin disorders.



Removal of underarm hair by shaving, plucking or waxing can lead to skin irritation and further pigmentation of this area.

# Behind the Research



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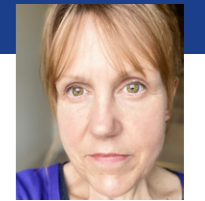


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## Research Objectives

The researchers investigate the pivotal role of store-operated calcium entry (SOCE) in maintaining skin health.

## Detail

### Bio

Unilever is a consumer goods company with an established portfolio of global brands in the Beauty and Personal Care sectors. Unilever has established a global capability in Human Biology Research – a group which works internally and with a diverse range of leading academic and commercial partners

to understand the functional biology of various skin sites across the human body. Partnering with experts in the fields of bioinformatics, molecular biology, and membrane biophysics, the group is building a unique understanding of skin and the appendages contained within it and how their biology changes in response to a range of skin conditions, including

dry skin, ageing skin, skin darkening, and the occurrence and consequence of sweating.

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## Personal Response

### What inspired you to conduct this research?

Since calcium ions and the process of store-operated calcium entry (SOCE) are central to the healthy functioning of many cell types, we were keen to understand their role in skin. We were amazed to see how pivotal SOCE, and key proteins STIM and Orai (named after the 'keeper of heaven's gate' in Greek mythology due to their vital role) were in determining the condition of human skin, its colour, and indeed the sweating response that enables humans to temperature-regulate. This inspired us to undertake our work on the role of TRPC1 in keratinocytes, and additional future studies.

### How might a better understanding of the SOCE mechanism help in preventing skin conditions?

Understanding SOCE and the roles of different STIM and Orai isoforms in controlling key processes such as keratinocyte differentiation, melanogenesis, and sweat production will provide deep insights into the consumer-relevant outcomes of skin condition, skin colour, and sweating. It may be possible to generate cosmetic solutions which provide beneficial changes to these outcomes, or the insights that help design specific solutions to conditions which may be classified as being more severe.