Skin in the game: Procter & Gamble scientists identify and target a novel pathway involved in hyperpigmented skin spots in vitro.

Procter & Gamble scientists discover novel pathway causing skin hyperpigmentation

Every day, people around the world look in a mirror and notice a new speckle, dot, or splotch on their skin. Spots caused by hyperpigmentation—where an area of skin is darkened—affect all ethnicities, skin tones, genders, and ages, and can be a point of pride, frustration, or perplexity for the owner. For decades, scientists at The Procter & Gamble (P&G) Company, which owns several of the world's leading skincare brands including OLAY, have been trying to unravel the mystery of how hyperpigmented spots form and grow. Now they are closer to cracking a new code, thanks in part to the creativity of one scientist and a supporting cast of thousands of other scientists and engineers.

Tomohiro Hakozaki, a research fellow in P&G's Beauty Technology Division, has been singularly focused on skin pigmentation for almost his entire career. With a Ph.D. in dermatological science, Hakozaki has worked in various areas of skin biology and biometrics as he has sought to better comprehend the mechanism within skin cells that causes hyperpigmentation. "You might remember when you first see the spot on your face, and you react 'what's this?'" he says. "When we do consumer research, spots always pop up as a number one or two skincare concern. This is what motivates my life's work. My dream is to develop the technology to fade and ultimately remove unwanted spots."

To find a solution to stop the spots, P&G scientists leveraged their knowledge about skin and pigmentation. While human skin color has several components, the biggest driver is melanin, and when it is localized in some areas, it appears as a spot. Melanin is produced in melanocytes, very specialized skin cells with dendritic properties: In the human epidermis, one dendritic melanocyte interacts with about 36 keratinocytes (another type of skin cell) and supplies them with melanin. We know that the presence of hyperpigmented spots is influenced by multiple intrinsic and extrinsic factors, such as ultraviolet B (UVB) exposure, hormone imbalance, inflammatory status, and aging; there has also been abundant research on the factors influencing melanin pathways, which include melanin synthesis, melanogenic cytokines, and melanosome transfer. However, the precise mechanism underlying melanocyte dendricity, or branching, has not been clear—until now.

The P&G team discovered a novel correlation between the presence of spots and an increase in the dendricity of melanocytes through comparing spot area versus nonspot area in multiple types of facial spots, including melasma, solar lentigo, and postinflammatory hyperpigmentation (PIH)/acne marks. The findings, which indicate that "increasing the export network of melanosomes may be a key common mechanism for increased pigmentation in spots," were reported in their groundbreaking paper for the *Journal of the European Academy of Dermatology and Venereology*. In essence,

Tomohiro Hakozaki

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the greater the dendricity, the more channels there are for melanin to be deposited on the surface of the skin. And the team uncovered another fascinating correlation: a link between the proinflammatory protein high mobility group box 1 (HMGB1) and "skin pigmentation machinery." Indeed, this pesky protein is a key contributor to stimulating formation of melanocyte dendricity.

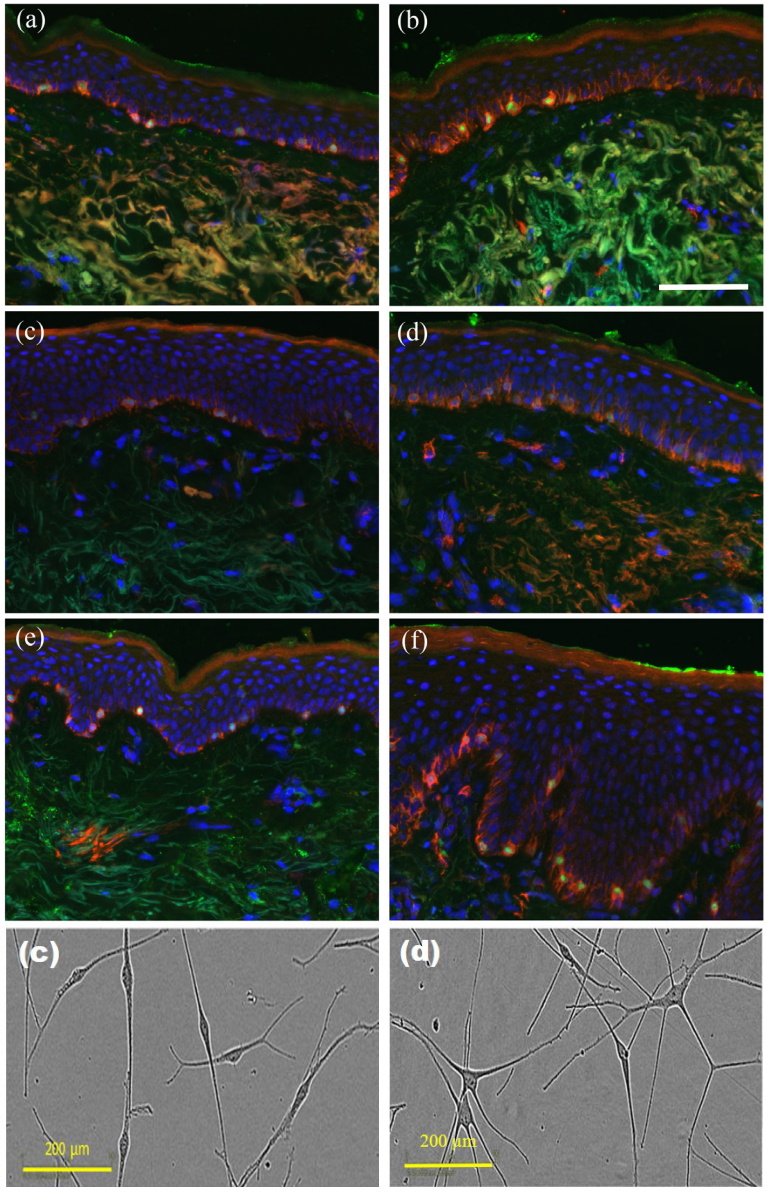
With this discovery, the P&G team aimed to examine what compound could potentially suppress the development of this dendricity in vitro. In collaboration with a supplier, they identified a special ratio of sucrose dilaurate (SD) and sucrose laurate (SL) in combination, called SDL; these two compounds have been used for years as emulsifiers, dispersants, or stabilizers in cosmetics, foods, and pharmaceuticals, with no safety issues. However, the team demonstrated that the SDL combination produced a "stabilizing" effect—a marked reduction of HMGB1 release, and a significant decrease in melanocyte dendricity formation and a reduction of dendrites already formed. "SDL can effectively stabilize the melanocyte from the root, which is a breakthrough in vitro science discovery in the industry regarding the spot-fading mechanism," Hakozaki notes. Moreover, SDL also reduces the melanosome transportation machinery protein Rab27a through the dendrite tips within melanocytes in a coordinated manner, inhibiting melanin production and transfer and lowering the total melanin amount in the epidermis.

"To prove this, we did a lot of sequential in vitro experiments," Hakozaki says. "There are many ways to reduce melanin production. Most of them relate to melanin synthesis. This is the only one we found so far to modulate the melanocyte dendricity effectively. So [for me] it was a 'holy cow' moment as a team member!"

This advancement has the potential to create whole new branches of technology. "Human biology is so complex," Hakozaki says. "We believed there should be much more, some other mechanism involved here." And now that they know what that mechanism is, scientists can develop new technology for targeting spots. For example, P&G has been adding SDL to niacinamide (a.k.a. vitamin B3), an invention that has recently been granted a U.S. patent.

It makes sense that P&G scientists would be the ones who unraveled the science behind spots. The company has always invested heavily in R&D and has pursued a science-first approach in improving people's lives.

There are still abundant opportunities to explore. "A spot is a very small place on your skin, but it involves very complex biology and pathways. What we have achieved is discovering a new intervention pathway in vitro," says Hakozaki. "But there is more to discover that can help the whole skincare industry in scientific research." He continues to be engaged and energized by this research. "I love my job," he says. "There is a saying that 'the only way to do great work is to love what you do.' If you haven't found it, keep looking. Don't settle. As with all matters of the heart, you'll know it when you find it. This is exactly what I have [found] here. It is really exciting to be working on cutting-edge science with thousands of talented people in specialties such as biology and beyond." Clearly, P&G values Hakozaki, because as he says, "the company has allowed me to stay focused in this field for more than a decade." And for an innately curious scientist, dedicated to improving the lives of people around the world, that hits the spot.



Immunofluorescence and cell culture studies from Procter & Gamble scientists show that increased melanocyte dendricity is linked to hyperpigmented skin spots and that a combination of sucrose dilaurate and sucrose laurate suppresses melanocyte dendricity in vitro.

PHOTO: ADAPTED FROM J. WANG *ET AL.* THE COMBINATION OF SUCROSE DILAURATE AND SUCROSE LAURATE SUPPRESSES HMGB1: AN ENHANCER OF MELANOCYTE DENDRICITY AND MELANOSOME TRANSFER TO KERATINOCYTES. *JEADV* 2022, 36 (SUPPL. 3), 3-11.