Unraveling the Mystery of Melanin

Does a tan protect skin from sun damage or contribute to it?

By CORINNA WU

Once, many people innocently enjoyed the lazy days of summer by working on a tan. A deep bronze tone, they believed, would act like a natural sunscreen, protecting their skin for the rest of the season.

Indeed more than a decade ago, test-tube studies on melanin, the modified protein that darkens skin, showed that it can block some of the harmful effects of ultraviolet radiation. Other studies, however, painted a less sunny picture of the dark protein. They indicated that melanin can itself play a role in certain chemical processes that damage DNA and other molecules in cells. This damage, some scientists speculate, is one of the mechanisms by which ultraviolet light can lead to skin cancer.

Chemists are now trying to determine what melanin actually does in the skin. Although most people have heard of melanin, scientists don't fully understand its structure and behavior, says John D. Simon of Duke University in Durham, N.C.

Melanin's photochemical properties might explain why certain people are more susceptible to skin cancer than others. People with fair skin and hair generally have a greater risk of skin cancer than do people with dark skin and hair. The incidence of skin cancer is 10 times higher in whites than in African Americans, for example.

By examining melanin's response to light in test-tube experiments, Simon and other researchers hope to reveal its true colors. "Is it photoprotective or photosensitizing?" asks Simon. "To some extent, both must be right."

K. Seidel

Red hair gets its color from the pigment pheomelanin. In the skin, this type of melanin protects people from sun damage, according to some research findings, and adds to the damage, according to others.

Even though people in the United States use more sunscreen than ever before, skin cancer rates continue to rise (SN: 6/6/98, p. 360). Melanoma, the most deadly form of skin cancer, is a disease of melanin-producing cells, or melanocytes. The American Cancer Society predicts that during 1999, 44,200 people will be diagnosed with melanoma and 7,300 people will die of the disease.

The tanning process begins in the melanocytes. Exposure to ultraviolet radiation stimulates these cells to produce tiny granules of melanin, which migrate into neighboring cells called keratinocytes. As old skin dies and new cells grow in from below, the newly pigmented keratinocytes work their way over 4 to 5 days to the topmost layer of skin. There they produce the color craved by sun worshippers.

Most ultraviolet light that reaches Earth is in the ultraviolet-A (UV-A) range, having wavelengths of 320 to 400 nanometers (nm). UV-A triggers the production of oxygen radicals, oxygen in a reactive form that can harm DNA and other molecules. Damaged DNA can then spur the rapid, abnormal proliferation of cells that characterizes cancer. In this way, UV-A might initiate the various types of skin cancer.

Because melanin can absorb UV-A and is present in melanocytes, scientists speculate that it might play some role in promoting melanoma. Also, melanin that has traveled into keratinocytes could contribute to basal cell and squamous cell skin cancers, which arise in those cells. These cancers are more common than melanoma but are much more treatable.

A second form of ultraviolet light reaches Earth's surface in lesser amounts than UV-A. Ultraviolet-B light (UV-B), with wavelengths of 290 to 320 nm, doesn't penetrate skin as deeply as UV-A light does, but it's more damaging to the cells that it reaches. UV-B directly alters cell structures and DNA. Exposure to UV-B leads to the full range of skin cancers, including melanoma.

Melanin is difficult to study because it has no unique chemical composition. "Saying 'melanin' is like saying 'wood,' explains Daniel C. Liebler of

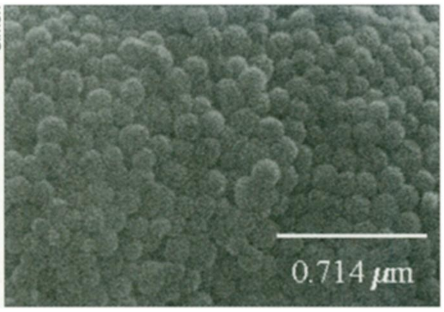
Science Service, Inc. is collaborating with JSTOR to digitize, preserve, and extend access to *Science News*.
www.jstor.org

the University of Arizona in Tucson. "There's a lot of different kinds of wood, and one tree's wood is a little different from another's."

Scientists know that all melanin molecules consist of long chains made mostly of derivatives of the amino acid tyrosine, but the individual units of the chain connect in random order. Melanocytes produce two distinct classes of melanin. Pheomelanin, which is red to yellow in color, contains the amino acid cysteine, which crosslinks with itself in the polymer. Eumelanin, which is dark brown to black, lacks cysteine. Light-skinned people generally have a greater proportion of pheomelanin in their skin than dark-skinned people do.

Studies on both the melanin types have yielded mixed results. Liebler finds most convincing the test-tube experiments with eumelanin that show that it has antioxidant properties. In other words, it

Simon



This scanning electron micrograph reveals that a melanin particle is made of many small pieces about 60 nanometers in diameter. Even sound waves cannot split apart the bits.

mops up reactive radicals that can damage cells and DNA. In this way, eumelanin appears to protect the skin from the oxidation that UV-A and UV-B can cause.

Some experiments on pheomelanin also have found antioxidant effects, while others indicate that it can promote oxidation. "Previous work had suggested that pheomelanin could be a wolf in sheep's clothing," says Liebler.

These findings prompted scientists to wonder whether the higher skin-cancer incidence in light-skinned people is due either to their shortage of protective eumelanin or an abundance of oxidizing pheomelanin.

To explore this question, Liebler and his colleague Ed S. Krol tested the melanins' ability to oxidize lipid molecules. They used commercially available eumelanin that had been collected from the ink sacs of *Sepia officinalis*, a squid-like mollusk commonly known as a cuttlefish.

The researchers extracted pheomelanin from red hair, which they collected from local barber shops and hair salons. "We said we needed the real thing—not tinted, not dyed," Liebler recalls. "We figured that only the hairdressers would know for sure." A pillowcase-full of clippings yielded a few grams of pheomelanin.

The Arizona scientists found that both forms of melanin protect lipids from oxidation. Even if the researchers saturated the test solution with oxygen, the protection persisted.

Melanins bind to a wide variety of compounds, including some drugs. Because of their affinity for melanin, drugs including antibiotics and antimalarials make skin burn more easily. In Liebler's experiments, the melanins' characteristics changed when the molecules bound metal ions such as iron, an element that is abundant in the body.

"If you add iron to the eumelanin, it goes from protective to being neutral," says Liebler, "but the pheomelanin reverted from being antioxidant to mildly pro-oxidant."

Pheomelanin's ability to become an oxidant doesn't prove that it's guilty of harming the skin, says Liebler. The results indicate, however, that the presence or absence of metals may explain the mixed results of earlier experiments. "Previous work probably didn't take into account whether there was iron contamination in their pheomelanin," Liebler notes.

While Liebler puzzled over the disparate findings on pheomelanin, Simon and his Duke colleagues J. Brian Nofsinger and Susan E. Forest turned their attention to eumelanin. Some past experiments had indicated that eumelanin can produce oxygen radicals, whereas others showed the chemical mopping up the radicals.

Other researchers had determined what wavelengths of light are most effective for causing eumelanin to generate oxygen radicals. They measured the amount of ultraviolet light absorbed by this melanin over a range of wavelengths, obtaining what's known as an absorption spectrum. They had also measured eumelanin's ability to generate oxygen radicals under stimulation from light of various wavelengths. Such studies yield a so-called action spectrum.

©John Forsythe/Univ. of Tex. Med. Branch, 1995

Commercially sold eumelanin is collected from the black ink of the European cuttlefish, Sepia officinalis.

In general, a substance is responsible for an observed chemical process when the action spectrum matches the absorption spectrum. With eumelanin, however, the spectra didn't correspond.

The Duke researchers wondered if the different sizes of eumelanin particles might explain the discrepancies. To find out, they tested eumelanin from *S. officinalis* and from eumelanin they synthesized chemically in the lab.

Previously, Lisa Zeise, Miles R. Chedekel, and their colleagues at MeL-Co in Orland, Calif., found that eumelanin particles from the cuttlefish are spherical and range in size from 70 to 460 nm in diameter. Half of the particles they measured were smaller than 140 nm.

By examining such particles under an electron microscope, Simon's group learned that eumelanin particles are made up of many even smaller pieces, each less than 60 nm in diameter. After the bits aggregate, the surface of an eumelanin particle looks like the bumpy, dimpled peel of an orange. Even powerful sound waves can't break the larger particles into their constituents, says Simon.

Simon and his coworkers used filters to sort eumelanin particles by size. They then determined the absorption and action spectra for the generation of oxygen radicals for each size eumelanin particle.

"The absorption spectrum changes dramatically with the size of the particles," says Simon. Moreover, the researchers found that the absorption spectrum of the smallest particles matched the action spectrum of unsorted eumelanin. These results suggest that the smallest particles are solely responsible for all of the radical production.

The size and shape of eumelanin particles in the body depend on the size and shape of the melanosomes, the organelles in melanocytes that synthesize melanin. In darker skin, the melanosomes are approximately twice as big as those in lighter skin.

Taken together, all these results leave open several possible explanations for melanoma's higher incidence among light-skinned people. These folks might produce less of the protective eumelanin. Or their smaller eumelanin particles may trigger more production of damaging radicals. If pheomelanin turns out to be harmful, its greater presence in light-skinned people might also put them at a disadvantage.

Until scientists can sort through this tangle, people shouldn't rely on melanin to protect their skin from the sun's rays. Best to leave that job to a shady tree, a long-sleeved shirt, and a wide-brimmed hat. □