Beyond Color and Beauty: Atomizing the Hidden Role of Skin in our Body

Dr. Umar Ahmad Sheikh

Affiliation:

Dr. Umar A Sheikh is currently working as a Postdoctoral Research Associate collaborating with Dr. Hao Chang in the Department of Dermatology – School of Medicine and Public Health at the *University of Wisconsin-Madison*. Dr. Umar was appointed in August 2022 and is working on projects that integrate biochemical and genetic approaches to dissect the genetic pathways that control skin development and disease. His appointment with *UW-Madison* will extend through mid-2025.

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It was cold and chilly on November 24, 2015, and temperatures had already started to drop, giving a sense of the arrival of winter in Kashmir in India, a beautiful valley in the foothills of the mighty Himalayas. I was travelling to another region of the state –Jammu – where winters are relatively warm compared to my home in Kashmir. I had to appear for an interview for the position of Research Fellow at the CSIR-Indian Institute of Integrative Medicine, which was my first professional introduction to the world of science.

As I was travelling from Kashmir, I was dressed in warm woolen clothes, but as soon as I entered the suburbs of Jammu, which I mentioned was relatively warm, I immediately started feeling the warmth of Jammu weather. I arrived at the interview venue early in the morning, and after waiting for some time, I entered the interview board room. Even before I took my seat, one of the professors on the interview panel started asking me, "Hey Umar, you are wearing warm and woolen clothes, but you are in Jammu. Can you explain to me why?" I immediately responded that I have come all the way from Kashmir where the winters are very cold, that is why I am wearing these clothes. He then again asked "what is it that makes us adjust to the environment we live in?" to which I replied that "it is basically the process of cellular homeostasis that makes us respond and adjust to changes in the environment we live in".

Co-incidentally, the project I was being interviewed for was also about understanding skin homeostasis. It happened to be the first indication that I would be studying skin homeostasis for my PhD, as I was eventually selected for that position, and started my research journey from there. As I started working in the lab, the intricate and hidden beauty of skin prompted me to pursue my research career understanding the diverse role skin plays in protecting itself and the whole body from outside environmental insults. In fact, skin is one of the very few organs in our body that works selflessly to protect other organs from different kinds of damage. Skin, which is the body's largest organ, is entrusted with protecting us from various environmental insults, including cold, heat, pollutants, toxins, pathogens, direct radiation exposure and many other things we encounter everyday just by going outside. Skin basically works as a bodyguard, sacrificing its own existence for the overall well-being of the body.

Throughout my research career, first as a predoc, continuing as a junior research fellow and exiting as senior researcher, I studied skin under diverse stressful conditions. I realized how beautiful skin is, and how important its functions are: acting as a physical barrier to pollutants and as an immunological barrier to external pathogens. I will mention here a few couplets: "A thing of beauty is a joy forever, everything has beauty, but not everyone sees it". These two couplets perfectly define the role and value of skin in our body. Skin is more than just beautiful, it plays a prominent and significant hidden role in our body, both at the micro as well as at the macro level, thereby keeping us safe and healthy. For me, the real beauty of skin lies in the hidden role it plays as a guardian of our body.

To simplify my PhD research for non-science audiences, I will start by describing the structural framework of skin. Skin has different kinds of cells in its different layers; these cells act as multitasking players. The different layers of skin work together as a functional unit, defending the skin itself as well as the internal organs from any external damage. Besides acting as a physical barrier to pollutants, toxins, dust, etc., the skin has a profound immunological role: to fight disease-causing pathogens. The immune system of the skin has elements of both the body's innate (non-specific) and adaptive (specific) immune systems. Skin harbors specialized immune cells that help fight invading microorganisms.

Skin also hosts a diverse community of beneficial bacteria, collectively known as the skin microbiota, which help keep us safe and secure. Despite these strict checkpoints, skin is routinely exposed to a lot of chemicals, toxicants, and carcinogens that prevail in the environment, impacting the skin's fundamental ability to protect us from those environmental insults. Excessive exposure to these environmental toxic factors can sometimes lead to fatal situations including melanoma, which is a deadly form of skin cancer. The biggest risk factor for skin cancer is excessive exposure to ultraviolet radiation (hereafter referred to as UV) that reaches the earth's surface from the sun. Nature has bestowed us with a defense system in the form of our skin, that keeps us protected whenever our body is exposed to these radiations.

Melanocytes are one type of cell present in the epidermis (outermost layer of skin) and hair follicles. The basic feature of these cells is their ability to produce a biologically important pigment called melanin, which protects the skin cells from the genotoxic effects of UV radiation. The color of skin is also determined by the amount of melanin these melanocytes produce, and the protection offered by the melanin is directly proportional to the amount of melanin produced in the cells. This protection by melanin is achieved by its ability to serve as a physical barrier that scatters UV light, and as an absorbent filter that reduces the penetration of UV through the skin epidermis, shown schematically in Figure 1.

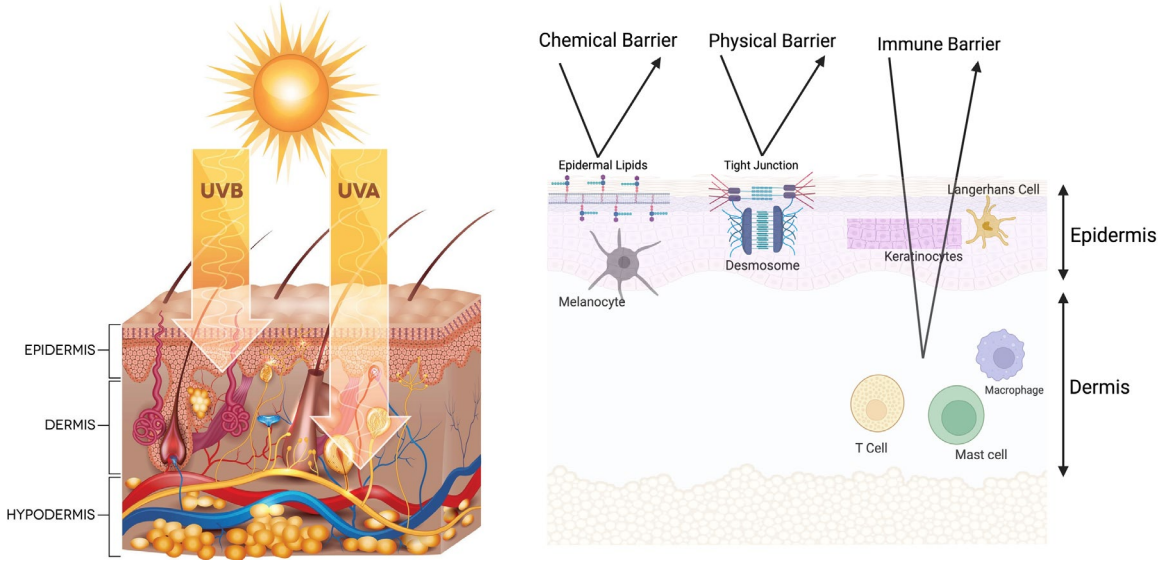

Figure 1: *Skin acts as a chemical, physical and immunological barrier to environmental pollutants, toxins, pathogens and UV radiation.*

Many epidemiological studies have shown a lower incidence of skin cancer in individuals with dark skin compared to those with fair skin. So, skin color, which is determined by the amount of melanin produced by the melanocytes, is a critical factor in protection against UV exposure. People with fair skin are at a higher risk of developing photodamage mediated skin cancers because their skin develops less melanin, whereas people with dark skin are at the lowest risk of developing skin cancer due to high synthesis of melanin by their skin melanocytes.

Skin cancer cases are increasing at an alarming rate globally, including in the United States. Scientists attribute this to various factors, including stratospheric ozone layer depletion. As per the American Academy of Dermatology Association, skin cancer is the most common cancer in the United States, and current estimates suggest that one in five Americans will develop skin cancer in their lifetime. It is estimated that approximately 9,500 people in the U.S. are diagnosed with skin cancer every day, and more than 1 million Americans are currently living with melanoma. These figures necessitate robust research into the factors that have led to the increase in melanoma cases.

As part of my PhD research, I tried to understand how cells in the skin respond to UV radiation exposure, and which signaling responses regulate the damage in the skin. I was also interested in understanding how cells under acute and cumulative UV exposure lose their natural ability to respond, increasing the chances of transforming a normal cell into a cancerous cell.

Previous research in this field has suggested that autophagy signaling is one of the critical cellular responses to UV damage. The word autophagy, derived from the Greek word for "self-eating", refers to the destructive metabolic process through which the cell turns over its own constituents and acts as a natural scavenger clearing any unwanted material from the cell. This is shown schematically in Figure 2. Autophagy also recycles the dead and diseased cells, generating energy to support cells at times of stress. It also resolves any sort of chaos that arises due to nutrient deficiency, genomic damage and instability.

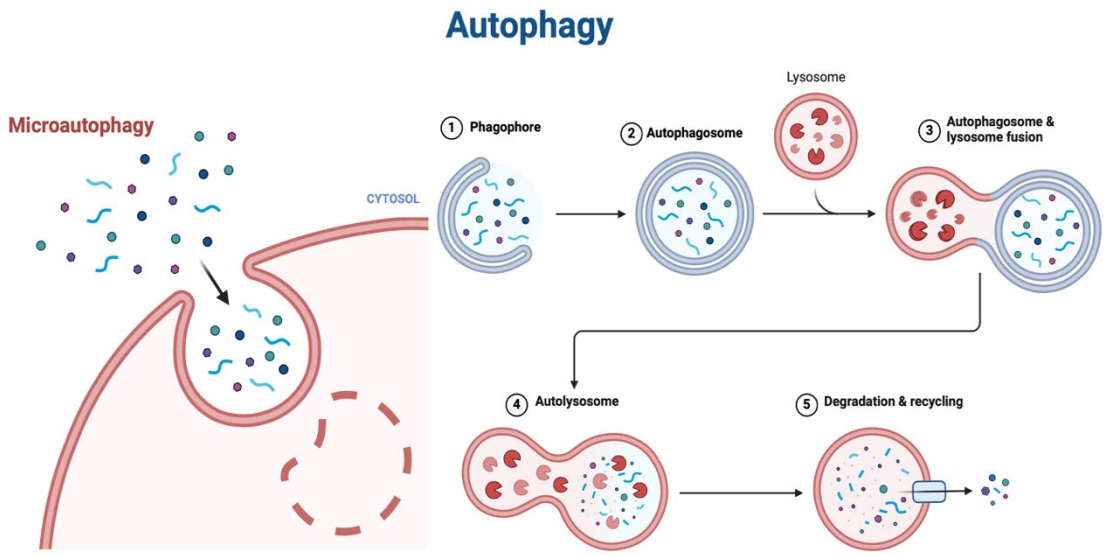

Figure 2: *Simplified illustration of how autophagy signaling process recycles the unwanted cellular residual materials, bacteria's and dead cells thereby producing energy that cells can use during times of stress, genome instability and nutrient deficiency. Small colored particles on the left side of the picture depict dead cells, bacteria, unwanted materials that need to be autolyzed as a routine cleansing process in the body and to replenish cellular energy reserves to be used during times of emergency.*

My Ph.D. research identified in part that excessive UV exposure to skin cells above the physiological dose (which is the dose we normally get exposed to) impairs autophagy signaling, thereby compromising the ability of skin cells to sustain their autophagy levels. This impairment in autophagy response makes the cells lose their natural ability to perfectly respond to UV insult, leading to an accumulation of damage that is the main causative factor in the transformation of a normal skin cell into a cancerous cell.

I tested one interventional strategy to externally, or pharmacologically, improve the autophagy signaling in cells, and I found that the cellular damage due to radiation exposure is significantly alleviated. I further explored this strategy as a therapeutic intervention by testing a natural product extract isolated from licorice plants. Topical application of this antioxidant significantly protected the skin cells, as well as mice's back skin, from the damaging effects of UV radiation, suggesting

that this molecule can be used in sunscreens as a safe alternative to metal-based sunscreens, which have some harmful effects on skin.

UV exposure has both positive as well as negative health effects on humans. One of the few positive effects is that our body heavily relies on UV exposure for synthesis of Vitamin D. An increase in skin cancer cases over the last 4 to 5 decades has raised various public health concerns among the scientific community and led international health organizations to develop and recommend strong sun protection measures to curb this sharp increase. However, at the same time, a growing concern about vitamin D deficiency, mostly in high-risk groups, is creating a kind of exposure dilemma. Current knowledge and understanding of the ambivalent effects of UV exposure necessitates a correct public health recommendation on optimal sun exposure based on scientific facts and reasoning.

To further carry on my interests and realize my research dreams, I joined the *University of Wisconsin-Madison* as a Postdoctoral Research Associate in August 2022, where I am currently involved in multiple research projects aimed at understanding skin development and disease. Research in my current lab is a step forward for me, and focuses on studying developmental biology to understand melanoma cancer genetics. We are focused on understanding the role of Planar Cell Polarity loss (hereafter referred to as PCP) in melanoma development and progression. PCP refers to the polarization of a field of cells within the plane of a cell sheet. PCP signaling leads to spatial differences in the shape, structure and function of cells in our body. To make it simple to understand, I will use the example of hairs present on our body. We see the hair on our body surface always tends to align in one direction, but not in the opposite, as shown in Figure 3. This is simply the effect of polarity. Also, the placement of eyes, ears, nose and other body parts is nothing but the polarization effect that happens during the development of an organism.

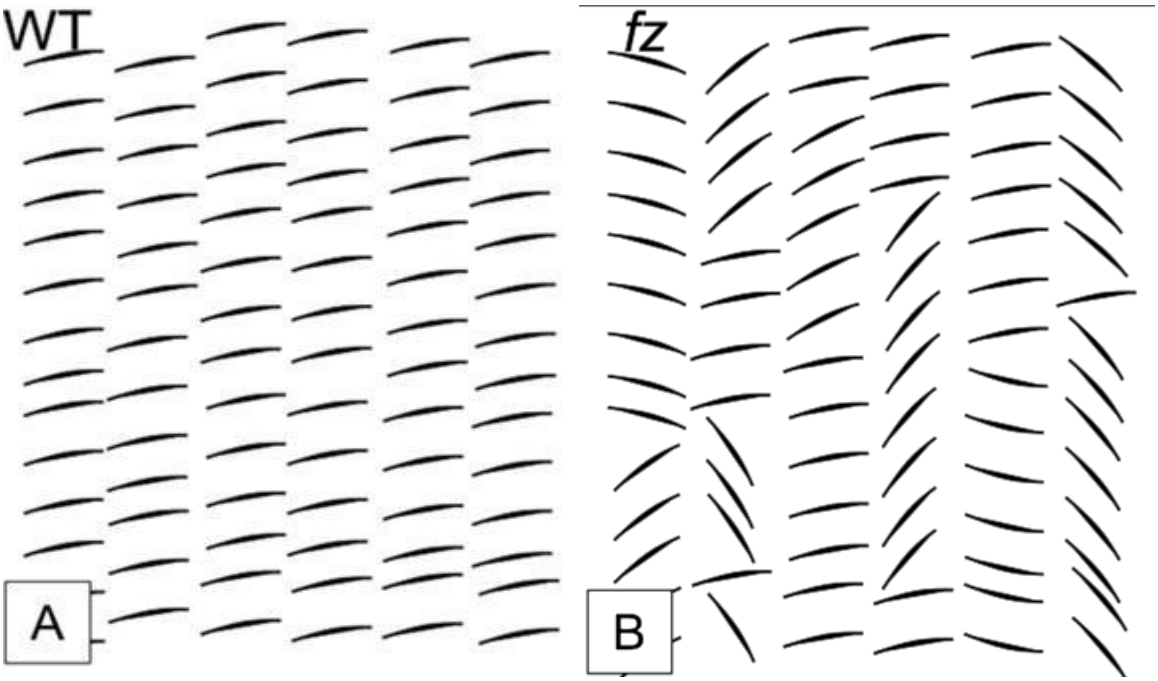

Figure 3: *Cartoon representation of Planar Cell Polarity in fly wing hair cells (A and B). Wing hairs point distally (to the right) in wild-type (WT) animals (A) but lose orientation in PCP mutants Frizzled gene (fz) (B).*

The PCP pathway is best known for its role in polarizing epithelial cells, which are among the most abundant cells covering the skin, body cavities, and blood vessels. The PCP pathway controls various intracellular processes and collective cell behaviors that are necessary for normal development, functioning, and maintenance of various tissues. Research suggests that the loss of PCP signaling plays a role in cell migration events during normal development and cancer metastasis. The cell migration process plays an essential role in the development and maintenance of multicellular organisms, tissue formation during embryonic development, wound healing and immune responses: each of these requires the orchestrated movement of cells in particular directions to specific locations. Cells often migrate in response to specific signals, which may be chemical or mechanical in nature. Any error during this process may have serious consequences, including tumor formation and metastasis. An understanding of the mechanism by which cells migrate may lead to the development of novel therapeutic strategies for controlling, for example, invasive tumor cells. By developing an understanding of PCP signaling and how PCP loss affects cell migration during cancer, researchers can use that information to devise suitable therapeutic targets against cancer.

Cell signaling is a critical way our cells coordinate growth and patterning of cells across the body axes, which is an imaginary line about which the body or a part of it rotates. Development of the body occurs in a nearly symmetrical fashion around this body axis. Growth and patterning are the two key events that govern the development of tissue shapes and structures in a complex organism. Cells are instructed by both quantitative and directional information during growth and patterning to achieve the desired shapes and cellular architecture required by many tissues and organs to function. This irreversible commitment of cells to achieve desired shapes and patterns is the reason the structural and functional framework of each cell and tissue is unique with respect to the rest of the body. Cell signaling is like a sophisticated communication network within our body, guiding cells in the growth and organization needed for organs to function properly.

Any small deviation from the natural behavior of cells can have devastating effects on the very development of the body. Previous researchers working on PCP, and the genes controlling this cellular mechanism, have found that mutations in the PCP genes cause many diseases in human patients and/or in mouse models, including cancer. Using routine and transgenic mouse skin as a model system, I and others in my lab are interested in dissecting the mechanisms of mammalian PCP and helping us better understand the development of PCP-related diseases. Transgenic mice are mouse models that have had their genomes altered by researchers to study gene functions. In these model animals, DNA from the mouse genome or from another species has been incorporated into each cell of the mouse's model genome. These models serve as the preferred choice to study the role of different genes in disease development and progression: by creating mutant forms of the respective gene in mice and then manipulating the mutant form, researchers like me can study the effect of gene deletion.

In my postdoc research, I am right now exploring the role of *Frizzled* receptor signaling in melanoma, which is one of the core components of the PCP pathway. Cells communicate with each other using chemical signals, which can be between proteins or other molecules in the cell. These signals are often secretory in nature and are released into the extracellular space once the stimulus is received by the cell. Once inside the cell, the signals are passed from one molecule to

another, like students passing notes in class, which results in a specific cell response which can be either cell division or cell death.

Cells have proteins called receptors that bind to signaling molecules and initiate a physiological response. For example, insulin receptors bind insulin to regulate blood sugar levels in the cells. Likewise, our body contains G protein–coupled receptors (GPCRs) which is a family of integral transmembrane proteins that mediate most of our physiological responses to hormones, neurotransmitters, and environmental stimulants. Frizzled signaling proteins are a class of GPCRs and are the cell surface receptors playing key roles in governing cell polarity, embryonic development, cell proliferation, and many other processes in developing and adult organisms. Mutations or abnormal *Frizzled* signaling response have implications in cancer growth and metastasis, which is the spread of cancer cells from the place where they first formed to another part of the body. In metastasis, cancer cells break away from the original (primary) tumor, travel through the blood or lymph system, and form a new tumor in other organs or tissues of the body.

Previous research in my current lab has identified a key gene in *Frizzled* signaling, *Frizzled6,* as having a role in melanoma metastasis. Our lab developed a knockout mouse model for *Fzd6* to precisely understand the role of this gene in cancer development and progression. Using this model, researchers in my lab have previously identified that knocking out *Fzd6* from mouse cells dramatically reduces the lung metastasis in melanoma, suggesting *Fzd6* as a potential target for devising suitable treatment strategies against melanoma. This is an ongoing project, of which I am a part, to further understand the role of *Fzd6* in melanoma and to explore it for therapeutic purposes. As there are 10 *Frizzled* signaling genes (*Fzd1-10*) that share a common structural and functional similarity, we were interested in dissecting and characterizing the roles of other *Frizzled* signaling genes in melanoma development and metastasis.

Using a series of cell-based and mouse models, I identified one more gene in this signaling pathway (name of gene is not revealed here as the research is unpublished yet) and I am right now actively working on it to unravel its role in melanoma development and metastasis. I, together with my research collaborators, am using multi-pronged strategies to identify which genes are linked to

skin cancer, and to explore those signals as they operate through and within the cells as suitable therapeutic targets in cancer.

Once the specific role of a particular gene is established through cell and animal model-based systems, these genes are then used as targets to develop specific drugs by manipulating the cellular signal they are part of. This whole process of drug discovery begins with the identification of a possible biological target which can be a biochemical entity, a protein, RNA, or, in this case, a gene. The developed drug preferentially binds to this target and elicits a physiological change in the cells that can kill the cell, like in the case of cancer.

Knowing that cancer is a global disease burden and is studied across the world, we at UW-Madison are working to understand how this disease develops and progresses and devise novel treatment strategies. Above all, we work to realize the Wisconsin Idea.

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