Melanin – a protector from skin cancer

Skin cancer is one of the most common malignant tumours worldwide. Epidemiological studies have determined that skin cancer occurs more often in people with lighter skin than those with brown or black skin. Ultraviolet (UV) radiation is the primary contributor to skin cancer development by causing DNA damage in skin cells called keratinocytes. Melanin, the pigment responsible for skin colour, also plays a role in generating so-called melanin caps – umbrella-like structures that protect the cells’ DNA from UV-related damage.

Melanin is the primary pigment in our body responsible for skin, eye, and hair colour. Our genetics mainly determine the amount of melanin in the body. Melanin also defends us against skin damage, including UV radiation. The pigment is synthesised by melanin-generating cells called melanocytes, and it is commonly transferred into cells called keratinocytes, a typical cell in the outermost layer of skin, the epidermis.

The Melanin Caps

In 1996, while a guest research fellow at the Department of Dermatology, University Hospital of Wales College of Medicine, UK, Dr Hongguang Lu and his colleagues observed melanin in keratinocytes from people worldwide. They found that melanin forms a cap over the nucleus in keratinocytes, where the DNA and genetic material are contained. These melanin caps reside at the skin surface and protect the keratinocytes from DNA damage caused by UV. Interestingly, these melanin caps are more common in people with darker skin. However, the mechanism behind the formation of the melanin cap is yet to be determined.

The quality and quantity of melanin and melanin caps vary between racial groups. People with heavily pigmented skin harbour more melanin caps compared to people with lighter skin, and this is associated with lower skin cancer incidence. Melanin cap formation is mainly related to skin colour or melanin pigmentation. However, how UV radiation or sunlight can cause a melanin response to form these melanin caps is not well understood in keratinocytes.

The Power of Light

All living beings on Earth use light photons from the sun as an adaptive advantage; for example, animals and humans use photons to help identify objects through their vision. UV radiation is composed of photons that activate receptors in the eye, called G-protein-coupled receptors (GPCRs) and downstream effectors. In most animals, light response pathways use a member of the opsin (OPN) family of GPCRs as a light detector. Over 1,000 OPNs have been identified in the animal kingdom. Some research suggests that these UV-sensing systems may also be present in the skin. One of these opsins, called OPN3, predominately expressed in the skin, has been found to be important in skin pigmentation regulation and even skin tumour progression. However, it is unclear if OPN3 is involved in the melanin cap formation as a response to UV exposure.

In a recent publication, Lu – now at the Guizhou Medical University in China – and colleagues demonstrated that OPN3 is critical in melanin cap formation and helps to protect the skin from damage like skin cancer. They have also determined the pathway by which OPN3 acts.

CAP FORMATION

Lu and his team found that different doses of UV radiation induce the expression of dynin, a transporter molecule in melanocytes that mediates the transport of melanin to keratinocytes. UV radiation also significantly upregulated proteins called α100 kDa (DCTN1) and Cytoplasmic dynein intermediate chains (Dync1i1) in human keratinocytes. These proteins are thought to facilitate the movement of substances within cells. To confirm whether DCTN1 is involved in UVA-induced keratinocyte melanin cap formation, researchers used small molecules called siRNAs to attach and downregulate DCTN1 levels in keratinocytes. Given UVA irradiation, the researchers observed that the formation ability of melanin cap reduced in the experiment group, suggesting that DCTN1 is an important factor in forming melanin caps in keratinocytes as a result of UV exposure.

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The research paves the way for OPN3 as a potential therapeutic target, protecting humans against UV-related DNA damage and, ultimately, skin cancer. However, they were unsure if the calcium signalling pathway is involved in the formation of melanin caps.

Before UVA exposure, they measured calcium levels inside (intracellular) keratinocytes. UVA exposure increases intracellular calcium and upregulated activation of CAMKKII and CREB. They found that silent OPN3 expression caused the amount of intracellular calcium to decrease in cells when exposed to UVA. Expression of calcium-related proteins was also reduced with the ceased expression of OPN3.

Calcium movement. Moreover, UVA exposure increased CAMKKII, CREB, Dync1i1 and DCTN1 levels, but this effect ceased when calcium release was inhibited, indicating that UVA mediates the PLCβ/calcium expression through OPN3.

Intracellular calcium movement activates the AKT pathway, which is important in recruiting the necessary proteins required for movement. One protein crucial in this pathway is Dync1i1. Lu and his team found UVA-induced AKT activation but not when OPN3 expression was silenced or when calcium release was blocked, indicating that UVA regulates the AKT pathway through OPN3/calcium signalling. Interestingly, AKT was important in the regulation of Dync1i1 and DCTN1 regulation, as UVA-induced Dync1i1 and DCTN1 expression was eliminated when AKT activation was blocked.

A BETTER UNDERSTANDING

Lu and his colleagues’ findings suggest that UVA-induced DCTN1 and Dync1i1 expression promotes the formation of melanin caps in keratinocytes that is completed via the OPN3/calcium/ Akt pathway. This research summarises that OPN3, a UVA photoreceptor, is vital in forming melanin caps in human keratinocytes. These findings expand our knowledge and understanding of the function of OPN3 and its role in the skin as a sensor for UV-induced melanin cap formation in keratinocytes. The research paves the way for OPN3 to be used as a potential therapeutic target, protecting humans against UV-related DNA damage and, ultimately, skin cancer.

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