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## **Shedding New Light on the Role of the Sunshine Vitamin D for Skin Health: The LncRNA-Skin Cancer Connection**

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### Abstract

Throughout evolution vertebrates including humans have depended on the sunshine vitamin D for their calcified skeletons. As our hunter gatherer forefathers ventured from the equator their skin tone became much lighter in order to permit an adequate amount of ultraviolet B radiation to enter the skin to produce the vitally important vitamin D. Although sensible sun exposure does not significantly increase risk of skin cancer it has remained a mystery as to why. Jiang and Bikle in their Viewpoint provide a novel insight as to how Mother Nature was able to balance the need for receiving adequate sun exposure to produce vitamin D while limiting damage caused by the DNA absorbing the UVB radiation. Long non-coding RNAs which are plentiful in cells have a dual personality. Some enhance malignancy while others act as tumor suppressors. Jiang and Bikle provide compelling evidence that these long non-coding RNAs in skin cells are responsive to 1,25-dihydroxyvitamin D<sub>3</sub> by decreasing their carcinogenic activity while enhancing their tumor suppression function presumably as a strategy for reducing ultraviolet-induced nonmelanoma skin cancer. Mother Nature got it right. Sensible sun exposure is important for maintaining an adequate vitamin D status. Once formed in the skin vitamin D can exit into the

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circulation to carry out its physiologic functions on calcium and bone metabolism. Some vitamin D however remains in the skin and is activated to interact with its vitamin D receptor to control cell proliferation using a variety of strategies including interacting with long non-coding RNAs to reduce risk of photocarcinogenesis.

Most vertebrates including humans have depended on sun exposure as their major source of vitamin D. This likely explains why there are so few dietary sources of vitamin D available since throughout evolution Mother Nature assumed that most humans would always be exposed to sunlight (1). Our hunter gatherer ancestors had deeply pigmented skin that was designed to be an effective natural sunscreen to reduce risk of skin damage from day long exposure to sunlight. However it also was engineered to permit enough ultraviolet B (290-315 nm; UVB) radiation to penetrate into the epidermis to produce the vital sunshine vitamin D<sub>3</sub> (2). This was demonstrated in Maasai warriors who were outside every day and maintained healthy blood levels of 25-hydroxyvitamin D in the range of 40-60 ng/mL (2). As our ancestors began migrating north and south they were less efficient in producing vitamin D<sub>3</sub> in their skin because of the increased zenith angle of the sun reducing the number of vitamin D producing UVB photons reaching the earth's surface (1). This would have led to vitamin D deficiency which had serious consequences for reproductive females. Vitamin D deficiency in utero and the first few years of life for females results in a flat performed pelvis with a small pelvic outlet making birthing complicated if not impossible (3). Even Neanderthals evolved a Celtic skin tone with the mutation of their melanocyte stimulating hormone receptor in order to produce enough vitamin D in their skin for healthy bone development and growth (4). Thus this was the likely evolutionary driver for reduced skin pigmentation as our ancestors migrated farther north and south from the equator.

For more than 40 years a campaign has been waged worldwide urging abstinence from direct sun exposure by stating that any sun exposure increases risk for skin cancer (5). Thus the general recommendation before going outdoors is to always wear sun protection. Since the function of a sunscreen is to efficiently absorb solar UVB radiation the proper application of a sunscreen with SPF of 15 and 30 absorbs about 93.3 and 96.7% incident solar UVB radiation respectively, thereby reducing the skin's ability to produce vitamin D<sub>3</sub> by the same amount i.e. ~93 and 96% (1). Unfortunately this message of abstinence from any exposure to direct sunlight has been embraced by health care professionals and the public leading to a worldwide vitamin D deficiency epidemic (6-9).

During sun exposure 7-dehydrocholesterol absorbs solar UVB radiation converting it to previtamin D<sub>3</sub> (10). Once formed in the lipid bilayer in the plasma membrane of the keratinocytes it is rapidly transformed into vitamin D<sub>3</sub> (1, 10). The vitamin D<sub>3</sub> that is produced in the outer lipid bilayer of the plasma membrane is released into the extracellular space where it is enticed by the vitamin D binding protein in the dermal capillary circulation to enter the bloodstream. Vitamin D<sub>3</sub> is first metabolized in the liver to 25-hydroxyvitamin D<sub>3</sub> [25(OH)D<sub>3</sub>] (7,9). 25(OH)D<sub>3</sub> then travels to the kidneys to be converted to its active form 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>] which is responsible for maintaining serum calcium levels and bone health (7,9,11,12). Many cells in the body including macrophages, colon, and breast cells have the enzymatic machinery to convert 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub> (12). Once formed this hormone has been reported to regulate cellular proliferation and differentiation, enhance bactericidal activity and modulate the immune system among other functions (1,9,11-13). Keratinocytes express both the vitamin D-25-hydroxylase and the 25-hydroxyvitamin D-1-

hydroxylase and have been reported to convert to vitamin D<sub>3</sub> and 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub> (14,15). Thus the vitamin D<sub>3</sub> produced in the inner lipid bilayer of the plasma membrane is released into the intracellular space and is likely converted to 1,25(OH)<sub>2</sub>D<sub>3</sub>. This hormone regulates keratinocyte proliferation and differentiation and has been an effective agent for the treatment of psoriasis (1,7). 1,25(OH)<sub>2</sub>D<sub>3</sub> also reduced ultraviolet radiation induced skin cell loss, DNA damage, immunosuppression and skin carcinogenesis (16). Improvement in vitamin D status markedly influences several hundred genes affecting up to 80 different metabolic processes including improvement in DNA repair and enhancing antioxidant activity which could help explain vitamin D's anti-cancer activity (17).

The Viewpoint by Jiang and Bikle (18) suggests that the skin cells have developed a clever strategy with the help of vitamin D<sub>3</sub> to reduce risk of malignancy from sun exposure.

Keratinocytes produce 1,25(OH)<sub>2</sub>D<sub>3</sub> may be reducing risk of skin cancer by interacting with its vitamin D responsive elements on long non-coding RNAs (lncRNAs). The plentiful lncRNAs in malignant cells can function as master regulators of cancer development that indiscriminately sustain tumor cell growth, enhance metastatic activity and angiogenesis (19). 1,25(OH)<sub>2</sub>D<sub>3</sub> is a potent inhibitor of cancer cell growth, angiogenesis and inducer of apoptosis (7,11-13). As suggested by Jiang and Bikle (18) their pioneering research has demonstrated how 1,25(OH)<sub>2</sub>D<sub>3</sub> counteracts the tumor inducing lncRNAs ability to enhance malignancy activity. However not all of the lncRNAs are bad news. Jiang and Bikle also found that many of the lncRNAs also have a good side i.e. that they have the ability to act as tumor suppressors and that 1,25(OH)<sub>2</sub>D<sub>3</sub> acting through its VDR helps to regulate the tumor suppressor activity of these lncRNAs. These novel observations and perspectives not only provide us with a new insight for how sensible sun

exposure reduces risk for skin cancer but may also provide an explanation for the many association studies demonstrating that vitamin D deficiency and inadequate sun exposure increases risk for many deadly malignancies (1,20,21). Mother Nature got it right. Sunlight has and likely will always remain as a major source of vitamin D<sub>3</sub> for most vertebrates including humans. The sun-induced production of vitamin D<sub>3</sub> in the skin is not only for the purpose of making a hormone responsible for calcium metabolism and other systemic functions but also serves as a sentinel within the skin cell to reduce risk of tumor formation due to the UVB induced DNA damage and increased oxidant activity both of which have been associated with increased skin carcinogenesis caused by excessive exposure to sunlight.

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