ACTA SCIENTIFIC CANCER BIOLOGY (ISSN: 2582-4473)

Volume 4 Issue 8 August 2020

Short Communication

Carcinogenicity of "Photoprotective" Skin-Pigments

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DOI: 10.31080/ASCB.2020.04.0243

Received: May 27, 2020

Published: July 17, 2020

Ultraviolet radiation (UV) from sunlight is a known carcinogen for skin cancers and skin is the largest human organ in direct contact with sunlight's UV. Majority of carcinogenic mutations induced by UV are the UV-signature, cytosine to thymine transitions, generated from the DNA adducts called Cyclobutane Pyrimidine Dimers (CPDs) [1-3]. Skin has specialized cells called melanocytes that produce melanin, a pigment known to be a potent shield against UV exposure. Contradicting the photoprotective properties of melanin, we discovered that melanin itself is oxidized by combinatorial activity of Nitric Oxide Synthase (NOS) and NADPH Oxidase (NOX). This oxidation produces Reactive Carbonyl Species (RCS) in excited triplet state that generate CPDs in complete absence of UV. The role of this pathway, which we named "melanin chemiexcitation" [4] remains under-represented in melanoma which is one of the deadliest of all skin cancer types.

UV exposure induces NOS and NOX activity in addition to inducing skin pigmentation as a sunscreen. This pigment is plausibly used as a raw material for ongoing melanin-chemiexcitation. This "loop" explains some contradictory aspects of melanoma biology. For example, why is melanin required for melanomagenesis [5] and why is melanoma spontaneously induced in an MC1R truncated, *BRAFV600E* mutated mouse models [6]? Besides the oxidative DNA damage held responsible in both the studies, we predict a predominant contribution from melanin-chemiexcitation mediated generation of mutagenic/carcinogenic CPDs. This is because we observed endogenous NOS and NOX activity in melanocytes, leading to ~ 3 fold higher CPD generation in dark (absence of UV) in case of the mice with golden fur (MC1R variants) [4]. Further, recently we discovered genomic sites that are ultrasensitive to CPD formation from direct UV exposure and indirectly through melanin-chemiexcitation [7]. Thus, melanin-chemiexcitation is a major contributor of melanomagenic DNA damage and melanomagenic mutations.

Carbonyl compounds have been detected in vivo and are known to be highly reactive. After losing their triplet energy to DNA and generating CPDs, the melanin-carbonyls produced by melanin-chemiexcitation will still be highly reactive. Carbonyls are known to deplete glutathione (GSH) [8,9] and we have observed reduced GSH/GSSG ratios in response to UV exposure, specifically in pigmented cells. Moreover, pheomelanin (golden pigment) synthesis consumes cysteine, which is an integral part of GSH, and the non-cancerous nevi (moles) are rich in pheomelanin. RCS are predicted to form adducts with DNA and proteins which are not well characterized so far. Such adducts can alter cellular physiology either through DNA damage/gene expression deregulation, or through protein dysfunctions. Notably, the chemical scavengers of carbonyl compounds are known to induce spontaneous apoptosis in melanoma.

In conclusion, it is evident that melanin-chemiexcitation pathway is a "non-classical" melanoma carcinogen. Contradictory to "sun-shielding" properties" we propose that melanin is also a central regulator of melanoma initiation and progression. We also propose a unidirectional positive loop in melanoma where, NOS and NOX mediated chemiexcitation generates carcinogenic CPDs, carbonyls derive melanoma through DNA and protein adducts, and NOS mediated promotion of melanin synthesis (not discussed here) provide melanin as a raw material for melanin chemiexcitation. Detailed investigation of melanin-chemiexcitation, melanin carbonyls, and carbonyl adducts with DNA and proteins will identify novel targets for new drugs against skin cancers including melanoma.

Acknowledgement

This work was supported by Institutional startup fund from Moffitt Cancer Center & Research Institute to Dr. Sanjay Premi.

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