Aspirin’s Protective Effects Highlight the Role of Inflammation in UV-Induced Skin Damage and Carcinogenesis

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In their article entitled “Aspirin protects melanocytes and keratinocytes against UVB-induced DNA damage in vivo,” Rahman et al. (2020) report that enterically administered aspirin attenuates UV-associated cell damage and in vivo UV-induced inflammation and squamous cell carcinoma. This report builds on prior studies from the Grossman laboratory that showed that aspirin inhibits many aspects of the malignant phenotype of melanoma (Kumar et al., 2018). Taken together, their findings suggest that aspirin might be useful as a UV-protective agent.

Inflammation has long been implicated in carcinogenesis, and inflammation is now considered one of the hallmarks of cancer (Hanahan and Weinberg, 2011). Rudolph Virchow, who many consider to be the father of modern pathology, was among the first to associate inflammation with cancer. In the mid-nineteenth century, he observed white blood cells (“lymphoreticular infiltrate”) in neoplastic tissues and suggested that cancer might develop at sites of chronic inflammation. Indeed, there have been many epidemiological, cellular, and molecular studies since then that support a link between inflammation and carcinogenesis. Ultraviolet radiation, widely considered to be the most important environmental carcinogen for skin malignancies, promotes the development of cancer through the production of mutagenic photolesions such as cyclopyrimidine dimers (CPDs) and [6,4] photoproducts in the DNA of keratinocytes and melanocytes in the skin. However, the bioactive consequences of UV extend far beyond its direct mutagenic impact on pyrimidine nucleotide bases in the genome. UV photons affect a myriad of biomolecules including lipids, RNA, and proteins and in so doing alter cell physiology. Above a certain threshold, the cellular and tissue damage caused by UV promotes a cascade of inflammatory responses in the skin, including the robust generation of ROS, the production of proinflammatory cytokines and mediators, vasodilation, activation of pain sensory pathways, and the recruitment of immune cells into the skin. Together, these physiological events define a sunburn, which represents a complex inflammatory response to UV exposure. What role does the inflammatory microenvironment have in carcinogenesis? The recent contribution by Rahman et al. (2020) suggests that inflammation contributes significantly to the process and that anti-inflammatory approaches might be a useful UV-protective and skin cancer—preventive strategy.

Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug widely used for its analgesic, antipyretic, antiplatelet, and anti-inflammatory properties (Abdelaziz et al., 2019). Indeed, some human population studies have implicated a protective role for aspirin or other anti-inflammatory agents in skin cancer prevention (Gamba et al., 2013), although others have not (Jeter et al., 2012), perhaps because of variability in its usage in large cohorts. Using cell and animal models, the authors found that aspirin reduced UV-mediated damage and inflammation as measured by sunburn cells (apoptotic keratinocytes), CPD load, 8-oxo-guanosine levels, and prostaglandin E2 levels. In the skin, aspirin reduced the inflammatory infiltrate following UV and promoted clearance of UV photolocations. Although they documented UV protection in Melan-A mouse melanocytes, aspirin did not impact latency or tumor burden in the TN61R mouse melanoma model based on expression of oncogenic NRAS (Hennessey et al., 2017). In contrast, aspirin had a clear protective impact on UV-dependent squamous cell carcinoma development in SKH1-E hairless mice.

The work by Rahman et al. (2020) should be viewed as proof of principle studies to show that aspirin reduces UV-mediated ROS and carcinogenic risk, at least for squamous cell carcinoma. Certainly aspirin has been widely used as a preventive agent against thrombosis, heart disease, and certain cancers; therefore, its potential use as a UV protectant may be reasonable. However, there are several important caveats and potential barriers that must be considered before aspirin could be translated into a meaningful anti—skin cancer or UV-protective product in humans. Can meaningful levels of aspirin metabolites be achieved in the skin? Can these levels be safely achieved via oral administration? Could aspirin be safely used in the pediatric population—a particularly UV high-risk population—when it has been associated with Reye syndrome in that age group? Could topical anti-inflammatory agents be developed as a UV protectant that
Clinical Implications

- Aspirin protected against UV-induced damage and inflammation in vitro and in vivo.
- Aspirin attenuated UV-induced keratinocyte carcinogenesis but did not impact UV-induced melanoma formation in mice.
- Through its anti-inflammatory properties, aspirin may be useful as a UV-protective agent.

could perhaps be incorporated into sunscreens?

Scientifically, the findings of Rahman et al. (2020) raise many questions. Does aspirin somehow prevent UV-mediated photoproduct development or does it also impact their repair? There are indications from the data in this paper that it might do both. Also, why didn’t aspirin protect against melanoma when it reduced photoproduct levels in Melan-A melanocytes? Was the lack of melanoma prevention because of the particular animal model that was used? In fact, one might expect that especially in melanocytes aspirin would be expected to lower CPDs caused by free radical–derived triplet state melanin (so-called dark photoproducts) because of its effects on reducing UV-induced ROS (Premi et al., 2015). I look forward to future work to clarify these issues and to possibly develop the use of anti-inflammatory agents in UV protection and skin cancer prevention.

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CONFLICT OF INTEREST

The author states no conflict of interest.

REFERENCES


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Phenformin: AMP(K)ed for Potential Repurposing

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The results in the article by Zhou et al. (2020) demonstrate that the antidiabetic drug phenformin inhibits skin tumor growth and promotes keratinocyte differentiation, and an underlying mechanism is also defined. In this commentary, additional potential mechanisms through which phenformin may exert its antitumorigenic effect are described. Thus, the proposed repurposing of phenformin to treat skin cancer has merit.


Skin cancer is the most common cancer in the United States, with about 3 million Americans affected by non-melanoma skin cancer (NMSC) each year (https://www.aad.org/media/statistics/skin-cancer). The two most common forms of NMSC are basal cell carcinoma and squamous cell carcinoma (SCC). With early detection and proper treatment, NMSCs have good prognoses and survival rates. However, this cancer can have a significant impact on QOL, and aggregate effects on mortality can be significant. Therefore, it is important to discover and implement new therapies to treat these skin cancers.

The article by Zhou et al. (2020) proposes the use of phenformin, a biguanide drug originally developed to lower blood glucose levels in patients with diabetes, for the treatment of NMSCs. These authors show that oral administration of phenformin abrogates the growth of developed tumors in the 7,12-dimethylbenzanthracene (DMBA)-12-O-tetradecanoylphorbol-13-acetate (TPA) initiation–promotion two-stage mouse model of tumorigenesis. Further investigation into the possible mechanisms by which this inhibition occurs is necessary to demonstrate that phenformin promotes the suspension-induced...