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Skin mutation burden drives adaptive immunity and response to immunotherapy

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ABSTRACT

Numerous studies over the past century have reported an inverse correlation between lifetime solar ultraviolet radiation (UV) exposure and all-cancer incidence and mortality. For decades, this relationship was hypothesized to reflect the action of photosynthesized vitamin D, though subsequent clinical trials have failed to demonstrate the expected anti-cancer properties. Rather than a consequence of vitamin D, I hypothesize that this inverse correlation reflects the immune stimulatory action of UV-derived skin neoantigens. Over time, such UV-mediated immune education drives immune repertoire diversification and superior adaptive immune responses to infectious disease and cancer. This hypothesis would explain the strong positive selection for light skin pigmentation following the out-of-Africa migration among humans inhabiting northerly latitude regions, and the longstanding racial disparities in cancer and infectious disease observed in North America. It suggests that the skin comprises an important reservoir of anti-cancer T cells that may be harnessed for anti-cancer therapy, and that skin mutation burden (SMB) may serve as a predictive biomarker of immunotherapy response. I propose a novel, non-invasive method for quantifying SMB as a biomarker.

Numerous studies over the past century have reported an inverse correlation between lifetime solar ultraviolet radiation (UV) exposure and all-cancer incidence and mortality.[1] This seemingly paradoxical observation reflects two distinct trends: (1) a negative correlation between UV exposure and the incidence and mortality of a broad range of solid tumors responsible for the great majority of human cancer, and (2) a weak positive correlation between UV exposure and the incidence and mortality of comparatively rare skin cancers. Fascinatingly, the same studies suggest that early-life UV exposure results in a lifelong reduction in cancer risk, implying the action of a long-lived anti-cancer factor.[2]

For decades, this relationship was hypothesized to reflect the action of photosynthesized vitamin D, spurring the exploration of vitamin D pathway agonists as anti-cancer therapeutics.[3] However, subsequent clinical trials have failed to demonstrate the expected anti-cancer properties of vitamin D, and to date, the US Preventive Service Task Force finds insufficient evidence to warrant vitamin D supplementation for the prevention of cancer.[4]

What, then, could explain this striking relationship? Rather than a consequence of vitamin D, I hypothesize that this inverse correlation reflects the action of an immune-mediated abscopal response to radiation: UV strikes the skin, damaging skin cell DNA and generating a multitude of neoantigens. These neoantigens—comprising both mutated proteins and unmutated, abnormally expressed proteins—are presented to the robust network of immune cells within the skin in a manner facilitated by the upregulation of cytokines, chemokines, and antigen presentation as part of the radiation damage response, ultimately resulting in the stimulation of antigen-specific T and B cells.[5] Over time, this UV-mediated immune education drives immune repertoire diversification and superior adaptive immune responses to antigen challenge (figure 1). The response is termed abscopal given that radiation strikes the skin, but the effect is observed throughout the body.

This immune education provides several advantages to the organism, foremost of which, from an evolutionary standpoint, is improved resistance to infectious disease. Infectious disease has historically been the primary cause of mortality, particularly for children and those of reproductive age. UV-mediated immune education provides a means to strengthen and diversify adaptive immunity without the risks and limitations inherent to building immunity through natural infection. The consequence is lower mortality from infectious disease, hence greater fitness. UV-mediated immune education would explain the strong selection for mutation-enhancing light skin pigmentation in humans who settled in UV-poor northerly latitude regions following the out-of-Africa migration, an occurrence which is otherwise poorly explained as an adaptation solely to facilitate vitamin D synthesis.[6 7] The hypothesis is supported by observations that

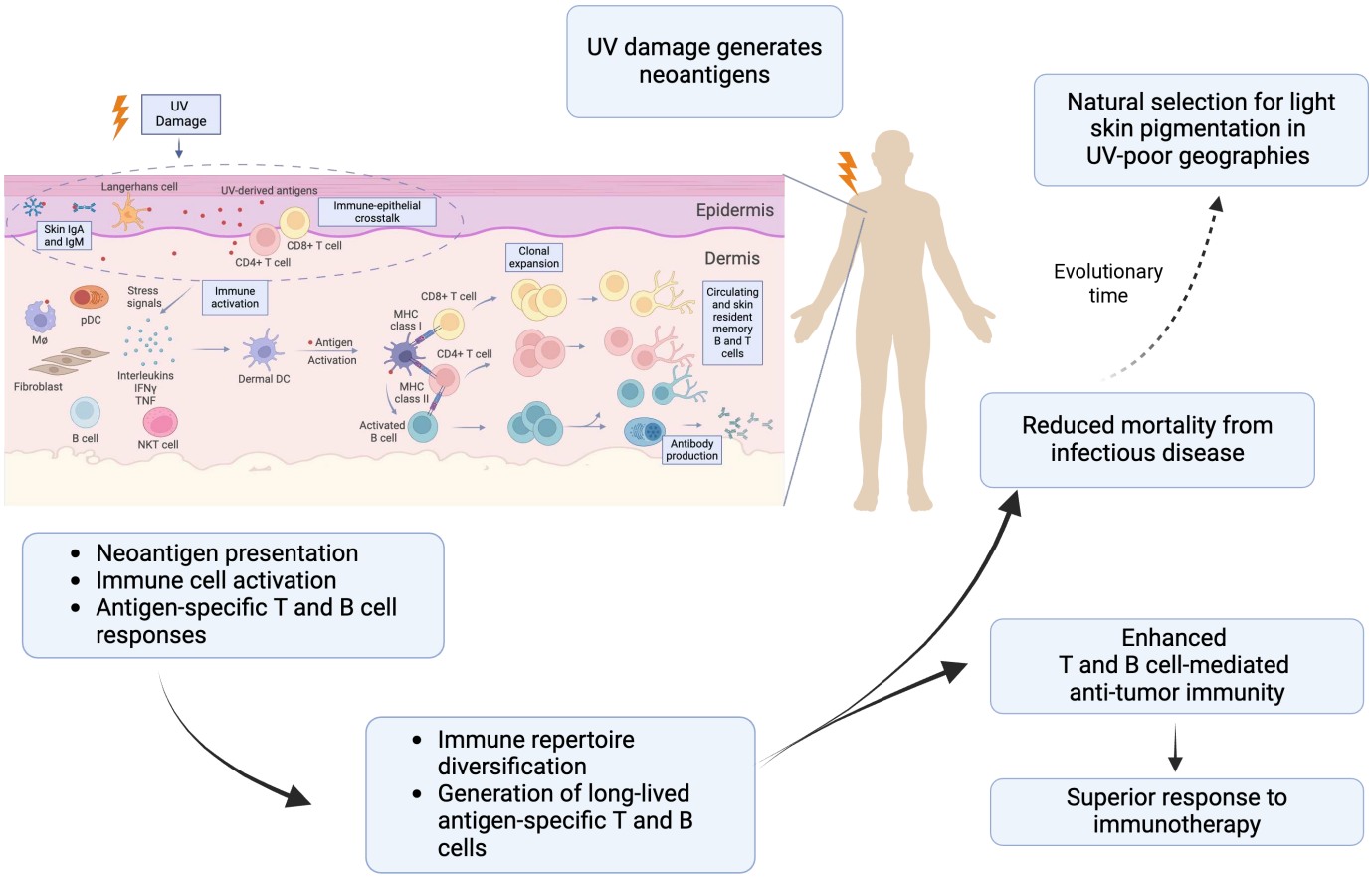

Figure 1 UV-derived skin neoantigens drive adaptive immune education. Solar UV-derived DNA damage gives rise to neoantigens in skin cells, resulting in the stimulation of antigen-specific T and B cells. Over a lifetime, such adaptive immune diversification reduces susceptibility to infectious disease and cancer and increases the likelihood of response to immunotherapy. The reduction in infectious disease mortality has driven selection for mutation-enhancing light skin pigmentation in humans inhabiting UV-poor geographies. DC, dendritic cell; IFNγ, interferon gamma; Ig, immunoglobulin; Mø, macrophage; MHC, major histocompatibility complex; NKT, natural killer T cell; pDC, plasmacytoid dendritic cell; TNF, tumor necrosis factor; UV, ultraviolet radiation. Created in BioRender. Looney, T. (2025) https://BioRender.com/z76k774.

phenotypically normal human skin may harbor many neoantigens in a manner dependent on underlying skin pigmentation and lifestyle,[8] and that skin neoantigens are able to efficiently elicit systemic T cell responses, as evidenced by the efficacy of skin scarification as a vaccination modality.[9] The hypothesis provides a biological basis for the disease-mediated decimation of Native Americans following contact with European settlers of North America, and the persistently elevated infectious disease mortality rate of US Blacks compared with Whites.[10] Beyond reducing the severity of infectious disease, UV-mediated immune education may be powerful enough to elicit sterilizing immunity against a previously unencountered pathogen in a subset of the population; such a possibility is implied by the exceptionally high prevalence of HIV among Blacks living in Southern Africa—where UV intensity is similar to that of Southern Europe—compared with Blacks living in Equatorial Africa (up to 30% vs 1%).[11]

A secondary advantage of this immune education is improved recognition and destruction of cancer. It may be considered secondary in that it likely has been a minor driver of selection for light-pigmented skin, given that natural selection inefficiently acts on traits affecting diseases that tend to occur after reproductive age, as is the case for most cancer. UV-mediated anti-cancer immunity would explain the persistent racial disparities in US cancer incidence and mortality, particularly the elevated incidence of breast, colon, and prostate cancer—among the most UV-sensitive cancers as determined by ecological studies—in Black versus White Americans. It would also explain the growing body of evidence suggesting reduced efficacy of immune checkpoint inhibition immunotherapy (ICI) in Black versus White Americans.[12]

Taken further, it is reasonable to believe those whose skin has accumulated the greatest number of mutations—and thus have the most developed anti-cancer adaptive immunity—are also those most likely to respond to cancer immunotherapy. This possibility is supported by several observations within the immuno-oncology literature. First, cutaneous immune-related adverse events (irAEs) associate with favorable response to ICI.[13] Cutaneous irAEs may reflect immune recognition of UV-derived neoantigens in phenotypically normal skin following loss of tolerance due to ICI, with the likelihood of a cutaneous

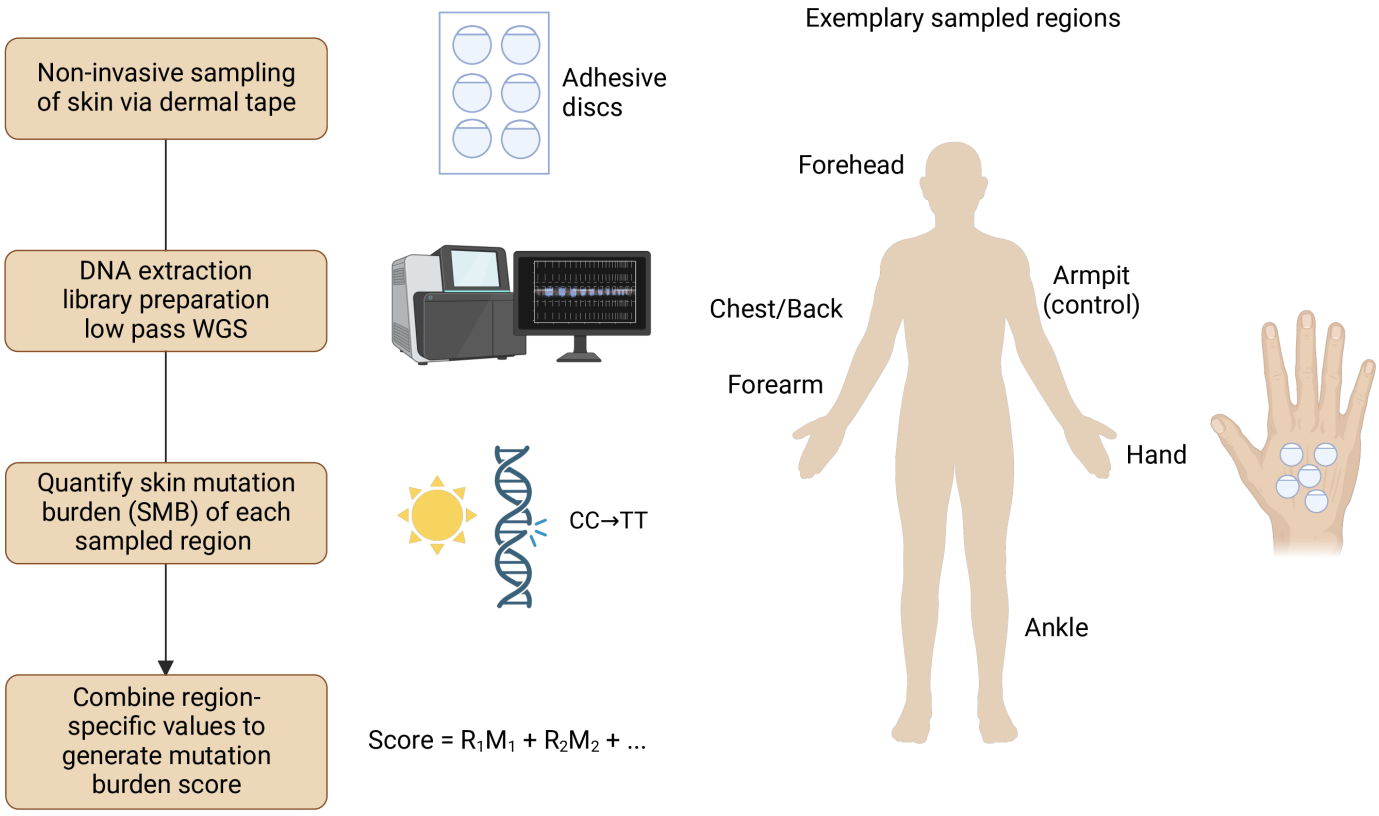

Figure 2 Non-invasive measurement of SMB as a biomarker. Skin cells are collected from one or more sun-exposed regions of the body and optionally a sun-protected region (eg, armpit) via dermal tape. For each sampled site, DNA is extracted, then analyzed via low-pass whole genome sequencing (WGS) to quantify the frequency of ultraviolet radiation (UV) damage-specific pyrimidine dimer mutations (CC>TT) at each sampled region. The mutation values from one or more sun-exposed regions are combined to produce a mutation burden score reflecting the extent of UV-driven adaptive immune education in the individual. To facilitate genome-wide association studies, the assay may also report genotype. Created in BioRender. Looney, T. (2025) https://BioRender.com/g72w344.

irAE proportional to the neoantigen burden at a given site; this would explain the tendency for cutaneous irAEs to involve sun exposed parts of the body such as extremities. Second, current or previous smokers respond more favorably to immunotherapy than never-smokers, across all cancer types and treatment modalities.[14] Analogous to UV mutation of skin, smoking generates an abundance of neoantigens in the normal lung epithelium which are presented to resident immune cells and strengthen adaptive immunity. Third, tumor mutation burden (TMB) as a predictive biomarker of ICI response has divergent predictive value across cancer types and is most predictive of response for cancers related to chronic mutagenic exposure such as non-small cell lung cancer and melanoma.[15] For such mutagen exposure-driven cancers, TMB inadvertently reflects the mutation burden of the mutagen-exposed normal tissue, making the reading more indicative of the organism-wide extent of adaptive immune education. Lastly is the observation that individuals harboring germline loss-of-function mutations in DNA damage response and DNA mismatch repair genes tend to respond more favorably to immunotherapy[16]; analogous to smoking, such germline loss-of-function mutations increase the organism-wide mutation burden, leading to enhanced adaptive immune education, and superior anti-cancer immunity.

If light skin pigmentation is indeed an immune adaptation acting to reduce infectious disease mortality, one may wonder why all humans do not have light skin. The answer is that there is a significant downside to light skin: the action of repairing UV-mediated DNA damage temporarily depletes folate and vitamin B_{12}, resulting in a short-term reduction in fertility.[17] This explains the seasonality of births in the northern hemisphere, where the most common birth month is September, 9 months after the winter solstice.[18 19] In this manner, skin pigmentation is an example of a trait exhibiting antagonistic pleiotrophy, where light skin enhances resistance to infectious disease by facilitating adaptive immune education, while dark skin preserves fertility. The divergent skin pigmentations observed in human populations therefore reflect local disease pressure and UV exposure, the latter a product of local UV intensity and lifestyle.

Recognizing the role of the skin as a driver of adaptive immunity reveals new opportunities to advance human health. First, skin mutation burden (SMB) may serve as a predictive and prognostic biomarker for cancer immunotherapy, potentially enabling first-line immunotherapy

for cancers where current biomarkers fail to identify most responders. For vaccine and drug trials, measurement of SMB during patient enrollment will help to ensure that treatment and control arms are balanced, thereby eliminating a hidden and potentially confounding variable. For genome-wide association studies, methods that simultaneously capture genotype and SMB will facilitate discovery of causative variants, given that SMB values can be used to correct for an important source of environmental variation. To address these applications, I propose a non-invasive, dermal tape-based method to quantify SMB as an exploratory biomarker (figure 2).

More importantly, perhaps, are the implications for disease prevention and therapeutics. If differences in SMB drive racial disparities in cancer and infectious disease, then many lives could be saved simply by adopting public policy that encourages UV exposure for individuals with dark skin pigmentation who live in UV-poor geographies; prescribed UV radiation (eg, suntanning) could be explored as a neoadjuvant or adjuvant therapy for cancer or as a disease prophylactic. To this point, there is a dire need for low-cost methods to reduce the spread of HIV in Africa; there is likely no solution more cost-efficient than sunlight. The action of sun exposure to reduce cancer and infectious disease mortality naturally brings into question the benefit of government health policy prescribing sun avoidance and sunscreen usage, adherence to which may be driving recent increases in the incidence of many cancer types.[20] Beyond infectious disease and cancer, prescribed UV may also aid in the treatment or prevention of geographically clustered autoimmune disease such as multiple sclerosis. Finally, given that the skin comprises a potent pool of anti-cancer T cells, topical compounds may be developed to enhance the activity or alter the trafficking of skin-resident T cells as a novel immunotherapy modality.

In summary, solar UV shapes adaptive immunity, and in such manner has influenced human evolution and the course of civilization. We may now harness its mechanism of action for the betterment of humanity.

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