COMMENTARY

Ageing research: rethinking primary prevention of skin cancer

Nobody will argue the need for effective primary prevention of skin cancers, the most common of cancers in humans with light skin tone. Numerous campaigns, investigations and studies, mainly focusing on UV-protection, have been conducted with the noble goal of reducing morbidity, mortality and the socio-economic burden of cutaneous malignancies. Yet, can we claim a significant impact? While educational and behavioural interventions are believed to be the cornerstone of effective primary prevention, efficacy and long-term outcomes are controversial.[1,2] Efforts to improve, for example, the reach of and adherence to UV-protective measures range from simply banning artificial UV-sources like tanning beds for minors, and legally binding regulations for outdoor workers with excessive UV-exposure in some countries, to targeted social media adds and gamified face-apps individually predicting and visualizing the impact of UV-radiation over time.[3,4] However, there is no reason to believe that any of the current measures, as astute as they may be, will be sufficient to address the foreseen sweeping rise of skin cancers, particularly in ageing societies.[5] As highlighted in Fig. 1, preventing the negative effects of UV-radiation is both important and actionable[6]; however, external noxa are only one piece to the skin cancer puzzle. Epidemiological studies and data from national registries call out that older age is the greatest risk factor for skin cancers. While one can argue that old age is a surrogate for cumulative exogenous skin damage, there is mounting evidence that biological processes of skin ageing, which are independent of external factors, also play a substantial role in skin carcinogenesis. This commentary aims at being thought-provoking. It touches on selected endogenously triggered biological processes linked to ageing and cancer in view of potential future interventions for primary skin cancer prevention.

Ageing research and cancer prevention

Ageing and age-associated diseases are often referred to as fate, being inevitable, or even natural. Yet, technically suffering from dysfunctional, ageing tissues and organs is about as natural as suffering from appendicitis or skin cancer. Not too long ago, in the 1800s, appendicitis was a death sentence and cancers were treated by bloodletting; nowhere close to what we happily appreciate from modern medicine today. Still, viewing ageing as a disease and treating it as a disease is still considered science-fiction. This is deliberately provocative, for a good reason: Ageing is actually associated with specific cellular processes that just begin to be unravelled. The objective is nothing new with first explicit longevity research being conducted more than 50 years ago. What is new are today's technological advancements to understand and interfere with the biology of ageing, proving that we can indeed tweak or even reverse some ageing processes in various animal species. While it is unlikely that we can (or even should) aim at defeating human ageing for various reasons, modifiers of ageing will still be able to change both healthspan (the time we live without disease) and lifespan. After all, who would not agree to an additional 20–40 *healthy* years? Such advancements will be realized by a significant reduction of age-related diseases including the prevention of cancers. Why? Because there is substantial overlap between the hallmarks of cancer and the hallmarks of ageing.[7,8] Thus, addressing biological changes of ageing will also address prerequisites of cancerogenesis. Effective primary skin cancer prevention needs to focus on both exogenous noxa like UV-radiation and pollution, as well as endogenous, ageing-related risk factors including senescence, mitochondrial dysfunction and impaired autophagy among others. This task is nothing short of a feat, as it is evident that the biology of ageing is complex: Individuals age differently, and even organs and organelles within one individual age differentially. It appears obvious that there will be no silver bullet to solve it all. Instead, personalized combinations of interventions will be required to achieve a positive causatum. Breaking this big problem down into many smaller problems is the way to start.

Senomorphics and senolytics

The posterchild of an ageing cell is a senescent cell, a cell in permanent cell cycle arrest that is still metabolically active. Today, we know several flavours of senescence including replicative senescence, and senescence due to genotoxic stress, oxidative stress, oncogenes or dysfunctional mitochondria. Today, it is well known that such senescent cells contribute to skin cancer development through a senescence-associated secretory phenotype (SASP) creating a smouldering, tumour-promoting inflammation, which in the context of ageing is often referred to as 'inflammaging'.[9] Eliminating such pathological senescent cells has been shown to significantly reduce the onset of skin cancers in animal models.[10] It is likely that future compounds eliminating senescent cells, so-called senolytics, or compounds neutralizing the SASP, so-called senomorphics, will positively affect skin cancer incidence and, as a side effect, will lower the risks for multiple other age-related diseases.[11] However, senescence is involved in more than just pathological inflammation. It also plays an important role in development, wound

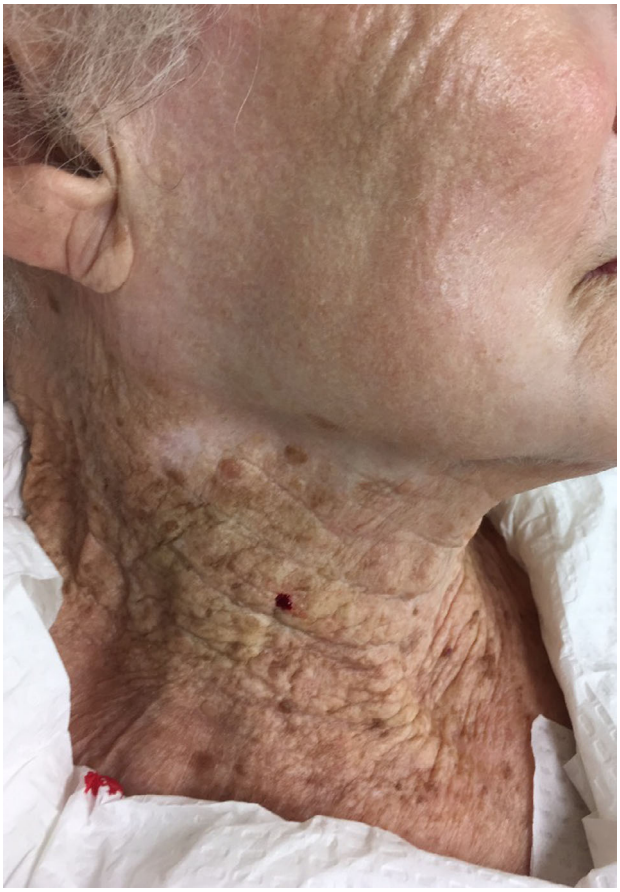

Figure 1 Cheek and neck of a 92-year-old female, who used UV-protective moisturizers on her face but not on the neck for 40+ years. Clinical examination reveals a striking difference in solar damage between her cheek and neck.

healing, tissue homeostasis, and in tumour suppression by virtue of, for example, oncogene-induced senescence. This complicates the search for compounds selectively targeting inflammatory senescent cells with damaging properties. Intermittent elimination of senescent cells in the elderly might be a path forward.

Protect, repair and reverse

The accumulation of DNA damage is a well-established risk factor for skin cancer. At younger age, we are typically well equipped with repairing such damage, or if repair is impossible, sending cells into apoptosis and clearing them through the immune system. The DNA damage repair (DDR) machinery is an orchestrated, lesion- and cell-specific, energy and substrate consuming biological process. Dermatologists are well aware of the x-fold increased skin cancer risk in patients with impaired DDR as, for example, observed in young patients with xeroderma pigmentosum. The best-known inducer of DNA damage in the skin is UV-radiation. However, and especially with older age, cell-intrinsic oxidative DNA damage, for example, due to dysfunctional mitochondria significantly contributes to a constant rise in single-strand breaks in (senescent) epithelial cells setting the stage for keratinocyte cancers.[12] At the same time, the ability to respond to DNA damage decreases with lower PARP1 and SIRT1 expression, as well as reduced levels of their substrate NAD^+ in older tissues.[13] Interventions aiming at improving and maintaining efficient DDR throughout life will protect from, and repair most acute genetic damage. To date futuristic, but far from impossible, seems the idea to also reverse established damage in older individuals or correct germline variants in syndromic disease using gene-editing technologies.

Conclusion

Ageing is a discrete and potent inducer of skin cancers that needs to be addressed systematically for improving skin cancer prevention in the future. Whether such measures will be individual decisions in the form of drugs and supplements, or if we will see the augmentation of foods and drinking water similar to the addition of iodine to salt, or fluoride to tap water, will be up for debate. Focusing efforts on both exogenous and endogenous risk factors for skin cancer development has the potential to reduce incidence at unprecedented rates, but the fact remains: people will continue to get sick and develop skin cancers, no matter how hard we try to prevent them. For this reason, it is important to emphasize that measures to improve public health aim to optimize tumour prevention at scale; this is different from ameliorating personalized treatment strategies for individuals with active (skin-)cancers.[14] Both propositions are equally important. It is only by developing treatments for ageing to advance primary skin cancer prevention, coupled with improving therapy for established skin cancers, that we can further optimize care.

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