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Fibroblast Senescence and Squamous Cell Carcinoma: How wounding therapies could be protective

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Abstract

Background—Squamous cell carcinoma (SCC), which has one of the highest incidences of all cancers in the United States, is an age-dependent disease as the majority of these cancers are diagnosed in people over 70 years of age. Recent findings have led to a new hypothesis on the pathogenesis of SCC.

Objectives—To evaluate the potential of preventive therapies to reduce the incidence of SCC in at-risk geriatric patients.

Materials and Methods—Survey of current literature on wounding therapies to prevent SCCs.

Results—This new hypothesis of SCC photocarcinogenesis states that senescent fibroblasts accumulate in geriatric dermis resulting in a reduction in dermal insulin-like growth factor-1 (IGF-1) expression. This lack of IGF-1 expression sensitizes epidermal keratinocytes to fail to suppress UVB-induced mutations leading to increased proclivity to photocarcinogenesis. Recent evidence suggests that dermal wounding therapies, specifically dermabrasion and fractionated laser resurfacing, can decrease the proportion of senescent dermal fibroblasts, increase dermal IGF-1 expression, and correct the inappropriate UVB response found in geriatric skin, thus protecting geriatric keratinocytes from UVB-induced SCC initiation.

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Conclusions—In this review, we will discuss the translation of pioneering basic science results implicating commonly used dermal fibroblast rejuvenation procedures as preventative treatments for SCC.

The translation of basic research findings into clinically useful therapies can be a long and sometimes arduous road. This review article highlights an example of an ongoing “bench-to-bedside” approach by linking the basic science of senescence and aging with a potential prophylactic treatment for squamous cell carcinoma (SCC). For decades, we have understood that the exposure of epidermal keratinocytes to UVB irradiation leads to a dose-dependent accumulation of DNA damage (1–6). Emerging *in vitro* basic research has uncovered the paramount importance of the insulin-like growth factor 1/insulin-like growth factor-1 receptor (IGF-1/IGF-1R) pathway in the response of skin keratinocytes to the ultraviolet B wavelengths (UVB) found in sunlight (7–9). We have demonstrated that the keratinocyte response to UVB exposure is determined by the severity of the DNA damage, whether the IGF-1/IGF-1R pathway is active or inactive during exposure to sunlight, and the cellular senescence profile of fibroblasts seen in aged skin (7–9). In particular, the abundant expression of IGF-1 in young adult skin is greatly diminished in geriatric skin. This loss of IGF-1 expression renders geriatric epidermis deficient in IGF-1R activation which leads to an inappropriate UVB response. Keratinocytes with IGF-1 in their environment respond to moderate UVB doses which induce DNA damage by becoming senescent (9–11). However, without IGF-1 these keratinocytes can continue to proliferate with DNA mutations which can result in premalignant cells. These critical observations have been made both *in vitro* and *in vivo*, leading to the development of new potential therapeutic targets (12–13). These new targets aim to treat the rising incidence of SCC in the geriatric population through wounding modalities designed to restore IGF1/IGF-1R pathways by reversing the fibroblast senescence phenotype. In this review we examine translational therapies being carried out *in vivo* which are based on the *in vitro* basic science research.

Involvement of age and UVB exposure in SCC pathogenesis

It is well established that the primary environmental factor influencing the development of skin cancer is exposure to the spectrum of ultraviolet wavelengths found in sunlight (1–5). Furthermore, there is a strong correlation between the development of skin cancer and increasing age (14–15). In fact, 80% of non-melanoma skin cancers (NMSCs) are diagnosed after the age of 60 indicating that age is a second major risk factor for the development of these skin cancers (21–23). However, the mechanism responsible for aging-associated NMSC has not been adequately defined. Epidemiological studies have reported that excessive sun exposure occurring in the first two decades of life can lead to UVB-induced mutations in clones of initiated keratinocytes (17–20). These clonal populations of altered keratinocytes persist in the epidermis and eventually obtain growth advantages through the accumulation of additional mutations in essential regulatory genes. The long incubation period between the original UVB-induced mutation and the development of a phenotypic NMSC is attributed to the time required to acquire the minimal number of chromosomal mutations that results in the appearance of a discernable tumor (17–20). This hypothesis relies on two assumptions: (1) the amount of sun exposure before age 20 is excessive; (2) the response of the skin to sun exposure remains constant throughout one’s lifespan.

However, recent studies have shown that these assumptions may not be entirely correct. These published reports suggest that nearly 80% of our lifetime exposure to sunlight occurs after the age of 18 (21). These data indicate that exposure to sunlight is relatively constant over our lifetime and not excessive in our toddler and adolescent years (21). In addition to this recent documentation of lifetime sun exposure, it has been well-accepted that the use of sunscreen can protect against AKs and NMSC in susceptible geriatric populations (22–24). These findings may suggest that the acquisition of actinic neoplasia is an ongoing process, a critical concept for future protective therapeutic strategies. Secondly, the ability to repair DNA damage diminishes as we age, both in general (25–26) and specifically in skin (27–28). Therefore, a UVB injury to keratinocytes obtained later in life may have different consequences and outcomes than UVB damage occurring earlier in life. Basic science ‘bench’ research has illuminated that one of the factors that accounts for differences in the UVB response in older populations is the IGF-1/IGF-1R signal transduction pathway (7–13). These recent findings have identified new concepts to treat pre-cancerous actinic damage by preventing the development of skin cancer in susceptible geriatric individuals. These new concepts were based on a correlation between the basic science findings and clinical observations and that increased cellular senescence along with inactivation of the IGF1/IGF-1R pathway occurs in aged skin. Additionally, these two observations are critical in the response (appropriate versus inappropriate) of keratinocytes to UVB exposure and propagation of DNA damage into pro-carcinogenic changes.

Involvement of aging dermal fibroblasts and reduced IGF-1 in NMSC pathogenesis

Our basic research findings are based on the stromal changes in aging skin which affects how keratinocytes respond to UVB irradiation. When the epidermis is exposed to UVB, the genomes of the epidermal keratinocytes become damaged (29). If this DNA damage is allowed to persist, alterations (or mutations) in keratinocyte genes will accumulate, leading to actinic neoplasia. Innately, keratinocytes have developed extensive protective measures to handle UVB-induced DNA damage. The IGF-1/IGF-1R signal transduction pathway in human skin is an excellent example of the interdependent relationship between the fibroblasts of the dermis and the keratinocytes in the epidermis. Human epidermal keratinocytes express the heterodimeric IGF-1R on their cell surface but they do not synthesize the corresponding ligand, IGF-1. Activation of the keratinocyte IGF-1R occurs primarily through the production and secretion of IGF-1 by papillary dermal fibroblasts. As dermal fibroblasts age and become senescent in vivo, their expression of IGF-1 is significantly reduced resulting in relatively inactive IGF-1Rs in geriatric epidermal keratinocytes. This reduction in the activity of the IGF-1R directly influences how geriatric keratinocytes respond to UVB irradiation. In young adult skin where IGF-1 expression sufficiently activates the keratinocyte IGF-1R, moderate levels of UVB irradiation lead to UVB-induced DNA damage that cannot be fully repaired which results in the keratinocyte becoming senescent. In this manner, the IGF-1R-dependent induction of UVB-induced senescence is a tumor evasion response which prevents keratinocytes from establishing UVB-induced mutations in proliferative cells without compromising the barrier function of the epidermis. However, in geriatric skin containing a significant proportion of inactive

IGF-1Rs, the same dose of UVB irradiation does not elicit the senescent response in keratinocytes and allows geriatric keratinocytes to replicate UVB-damaged DNA. Therefore, geriatric keratinocytes are not protected by the senescence-associated tumor evasion response and have an increased potential for mutated, replicating keratinocytes. Consequently, if the IGF-1/IGF-1R pathway is active during UVB exposure (with keratinocytes being exposed to adequate levels of IGF-1 from fibroblasts) three appropriate responses occur in order to prevent propagation of mutations and initiation of carcinogenic processes; (1) mildly-damaged DNA is completely repaired and the keratinocytes survive, (2) keratinocytes with extensively-damaged DNA that cannot be completely repaired are removed by apoptosis or (3) keratinocytes with intermediate levels of DNA damage that cannot completely repair the genome undergo stress-induced senescence which removes the cells from the cell cycle while still maintaining the integrity of the tissue (7–13). However, if the IGF-1/IGF-1R pathway is inactive during physiologically relevant sunlight exposures an inappropriate response occurs where keratinocytes with unrepaired DNA damage are able to continue proliferating with potentially mutated genes.

This *in vitro* ‘bench’ discovery that epidermal keratinocytes IGF-1R activation status is crucial in response to UVB, led us to postulate the clinical relevance of reduced IGF-1 expression and IGF-1R activation, and more importantly if this may be correlated to increased susceptibility of aging individuals to skin cancer *in vivo*. When comparing skin samples of young (<25 years old) and geriatric (>65 years old) volunteers, it was determined that geriatric skin accumulates increasing proportions of senescent fibroblasts (7–13). This increased proportion of senescent fibroblasts in geriatric skin leads to a decrease in dermal IGF-1 production and a corresponding deficiency in epidermal IGF-1R activation (3). The lack of IGF-1R activation during UVB exposure results in an inappropriate UVB response resulting in the occurrence of basal keratinocytes proliferating with DNA damage in geriatric skin (7). Most importantly, the injection of IGF-1 into the dermis of geriatric subjects prior to UVB irradiation restores the appropriate UVB response (7), indicating that the inappropriate UVB response could be overcome by increased activity of the epidermal keratinocytes IGF-1R.

These published data shed new light on the explanation for the increased incidence of SCC with age (14–16). This new hypothesis states that the selection of initiated epithelial cells is accelerated in aged tissue due to alterations in gene expression by senescent fibroblasts supporting epithelial cell growth (7–8). Specifically, this new paradigm indicates that the accumulation of senescent fibroblasts in geriatric dermis leads to a silencing of IGF-1 expression in the skin, resulting in a deficient activation of the IGF-1R in epidermal keratinocytes, causing an inappropriate UVB-response in keratinocytes. This IGF-1 deficient state results in the formation of leading to proliferating keratinocytes containing DNA mutations in response to relatively low levels of UVB exposure (~1 MED), and subsequently photocarcinogenesis (7–8). This new paradigm explains previous observations, such as the ability of sunscreen use to decrease actinic neoplasia in susceptible populations (22–24). Since UV light can also result in photo-aging with increased fibroblast senescence (and less production of IGF-1), this paradigm also explains how cumulative exposure of sunlight leads to actinic neoplasia. Given the findings that the lack of endogenous IGF-1 in

geriatric skin results in an inappropriate pro-carcinogenic response to low UVB exposure, which was reversed by local injection of exogenous IGF1; alternative prophylactic therapies to restore IGF-1 levels in geriatric skin were tested.

The theoretical basis for prophylactic wounding therapies to prevent SCC

Inasmuch as the increase in SCC incidence and its associated morbidity and cost make actinic neoplasia a significant disease process, the prevention of these tumors has clinical importance. Preventing cancers before they develop by targeting pre-cancerous changes is a very attractive and sometimes elusive goal. For patients with established AK precursor lesions, strategies include destruction by physical modalities such as cryotherapy (freezing), electrosurgery (burning), curettage (scraping), photodynamic therapy (PDT) with an adjuvant, or topical medicines such as 5-fluorouracil or immune-mediated destruction with topical imiquimod (33–38). Moreover, treatment of these early lesions is essential in order to prevent progression to SCC. Treatment for recurrent skin cancer is usually less successful than treatment for primary skin cancer. Most recurrences occur in the first 2 to 5 years; thus, patients with SCC need close monitoring, which results in increased costs to our healthcare system.

Though somewhat effective in treating established pre- or low-grade cancerous lesions, some of these treatment strategies are extremely disfiguring and place an enormous financial burden on our healthcare system. In addition, these treatments only target the pre-cancerous or tumor cells which may not treat the underlying process by which aged skin is more susceptible to neoplasia. If, as our research indicates, a major deciding feature of aging-associated SCC initiation is an inappropriate UVB response by geriatric keratinocytes due to the lack of IGF-1 and senescence status of geriatric dermal fibroblasts, then this provides the impetus for novel treatment strategies targeting senescent dermal fibroblasts (7–13). Therefore, treatment modalities which restore collagen expression, remove senescent fibroblasts, and recruit new fibroblasts thereby normalizing the secretion of IGF-1 could potentially prevent the initiation of UVB-induced carcinogenesis caused by ongoing sun exposure. As a result, studies using both dermabrasion (12) and fractionated laser resurfacing (13) have been pursued to determine if the dermal wounding response resulting from these dermal rejuvenation therapies can restore the appropriate UVB response in geriatric skin.

The use of dermabrasion and fractionated laser resurfacing to reverse senescent pathology

Dermabrasion, using #60 grain sandpaper to create a wound extending into the papillary dermis, was the first wounding modality tested. Non-diabetic geriatric (age 65 or greater) volunteers underwent dermabrasion to a 5 x 5 cm area of sun-protected buttock skin. After three months the subjects then were treated with 1 MED (approximately 350 J/m²) UVB to a 5 x 5 mm area of previously wounded skin or non-wounded skin on contralateral buttock skin. Twenty-four hours after the localized UVB irradiation, the subjects underwent punch biopsies of wounded unirradiated; wounded radiated, un-wounded unirradiated; and wounded irradiated skin. This study demonstrated that wounding via dermabrasion resulted

in less senescent fibroblasts and increased levels of IGF-1 mRNA levels (12). In fact, these values in wounded geriatric skin were similar to those found in skin from young (age < 30 years) subjects. UVB irradiation of unwounded geriatric skin resulted in the formation of initiated (UVB-damage in proliferating cells) basal keratinocytes. However, consistent with the normalization of numbers of senescent fibroblasts and IGF-1 levels, UVB treatment of previously dermabraded skin did not result in the formation of initiated keratinocytes. These studies provided the first evidence that wounding of geriatric skin could reverse this inappropriate pro-carcinogenic UVB response.

Although the results of these studies were exciting, the use of dermabrasion for wide-spread areas of skin as a prophylactic agent would not be very practical due to the significant morbidity of this treatment modality. To that end, the ability of wounding by fractionated laser resurfacing (FLR) to correct the inappropriate UVB response in geriatric volunteers was tested. Recently published studies (13) found that FLR treatment to both sun-protected buttock and sun-exposed forearm skin in geriatric volunteers resulted in similar decreases in numbers of senescent fibroblasts, upregulation of dermal IGF-1 levels, and normalization of the acute UVB response. Surprisingly, the effects of FLR were similar to that of the more invasive dermabrasion. That the relatively benign FLR procedure, increasingly used for its “cosmetic” effects, could also “normalize” geriatric UVB protection suggests that this modality can also protect against future actinic neoplasia (see Figure 1 for a cartoon describing the hypothesized protective effect of FLR on photocarcinogenesis). Ongoing studies examining the long-term effectiveness of these wounding modalities on dermal IGF-1 production and numbers of senescent fibroblasts are in progress, and preliminary studies suggest that these effects are still seen for at least two years following FLR (*unpublished results*).

Conclusions and Future Directions

Preclinical *in vitro* data leading to the ongoing *in vivo* clinical studies described in this review represent a new paradigm. These studies are exciting not only as they provide an explanation for SCC, they provide the impetus for novel interventions that could be used to prevent actinic neoplasia. At present, photorejuvenation therapies are gaining wide-spread acceptance to allow patients to appear younger. That these therapies can likely protect against future skin pre-cancers and cancers is a “nice bonus”. Future avenues of investigation, including following our cohort of laser-treated subjects longer, as well as examination of wounding in immunosuppressed populations who are at high-risk for developing SCCs. Going forward, the combination of chemopreventative (39–40) and prophylactic wounding therapies (41–45) could prove to be very effective at controlling the incidence of SCC in high risk geriatric individuals. These studies will provide well-characterized patient samples that will be useful for further in-depth studies evaluating the effects of dermal wounding in this population. The successful development of the prophylactic therapies described in this review may have a major impact on how SCCs can be prevented in susceptible individuals.

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Figure 1. The role of aging in photocarcinogenesis and the proposed prophylactic effect of fractionated laser resurfacing

This illustration compares the response of young skin and old skin to UVB irradiation and how the response is altered in FLR-treated geriatric skin. Features of the UVB response for each skin type is listed under the image.