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A New Paradigm for the Role of Aging in the Development of Skin Cancer

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TO THE EDITOR

Cancers of the skin are the most common cancers to afflict Americans in the United States with over 1,000,000 new cases estimated to occur in 2008 (ACS, 2008). The primary environmental factor that influences the development of skin cancer is exposure to sunlight, in the ultraviolet B (UVB) wavelengths. Notably, a dramatic increase in the incidence of skin cancers is seen with increasing age (ACS, 2008), as evidenced by the fact that a majority of skin malignancies are found in people over the age of 60 years (Kraemer, 1997; ACS, 2008). However, the mechanisms underpinning the correlation between age and skin cancer are not well understood. New ideas on the link between age and skin cancer have arisen based on age-related accumulation of stromal senescent cells that can lead to a tumor-promoting environment (Krtolica *et al.*, 2001; Krtolica and Campisi, 2002; Dilley *et al.*, 2003; Parrinello *et al.*, 2005; Collado *et al.*, 2007). Combining these recent data from others with data from our laboratory leads us to propose a new paradigm for the role of aging in the development of skin cancer involving the insulin-like growth factor-1 receptor (IGF-1R) pathway (Kuhn *et al.*, 1999; Chuang *et al.*, 2005; Heemst *et al.*, 2005; Kurosu *et al.*, 2005; Samani *et al.*, 2005; Lewis and Spandau, 2008; Lewis *et al.*, 2008).

The historical explanation for the correlation between skin cancer and aging is that UVB-induced skin damage during childhood and early adolescence initiates mutations in keratinocytes (Kraemer, 1997; Whiteman *et al.*, 2001; Krtolica and Campisi, 2002; MacKie, 2006; Feng *et al.*, 2007). Subsequently, these keratinocytes containing mutations acquire a growth advantage that over many decades generates enough genetic change to become carcinogenic. However, can we presume that time is the sole contributor to UVB-induced skin cancers? It is reasonable to consider that the physiology of aging also lends a hand to carcinogenic events. Recent data from a variety of labs have demonstrated a modification on the theory of skin cancer and aging based on changes in stromal fibroblasts of aged individuals. There are age-related increases in the number of senescent dermal fibroblasts and epidermal keratinocytes in human skin (Dimiri *et al.*, 1995). In a study involving aging primates, an age-dependent increase in markers of senescence in skin fibroblasts was observed (Herbig *et al.*, 2006; Jeyapalan *et al.*, 2007). Given this age-associated accumulation of senescent cells, it is reasonable to propose that cellular senescence may contribute to age-related cancers by altering the surrounding tissue into a neoplasia-promoting environment. The paradoxical effect of cellular senescence on an organism's well-being has been called antagonistic pleiotropy (Williams, 1957; Krtolica and Campisi, 2002). However, cellular senescence is a powerful tumor suppressor limiting cell life span and removing damaged cells from a proliferative state preventing formation of clonal tumors (Campisi, 2005; Hornsby, 2007; Rodier *et al.*, 2007). Conversely, the accumulation of senescent cells may contribute to aging and provide a tumor-promoting environment due to their altered properties such as stromal matrix reorganization and/or degradation, secretion of growth factors, and inflammatory cytokines (Krtolica and Campisi, 2002; Parinello *et al.*, 2005). Here we present our data proposing a new paradigm to explain non-melanoma skin carcinogenesis that further substantiates the importance of stromal interactions in the progression of carcinogenic events. The stromal interactions discussed demonstrate that IGF-1 and the IGF-1R are critical in the interactions between dermal fibroblast and epidermal keratinocytes and that they play an important role in aging and the response of skin to UVB irradiation.

Abbreviations: NMSC, non-melanoma skin cancer; UVB, ultraviolet B

The stroma and some basement membrane components are synthesized by stromal fibroblasts that also produce soluble factors that promote survival and growth of the skin. The health and proper functioning of the skin is highly dependent on the synergistic interactions between the dermal fibroblasts and epidermal keratinocyte. One factor regulating the interaction between dermal fibroblasts and epidermal keratinocytes is IGF-1 (Barreca *et al.*, 1992; Tavakkol *et al.*, 1992). In the skin, keratinocytes express the IGF-1R but do not synthesize IGF-1. Dermal fibroblasts support the appropriate development of epidermal keratinocytes by secreting IGF-1. The mature IGF-1R consists of four subunits, two identical extracellular α- and two identical transmembrane β-subunits linked by disulfide bridges. IGF-1, IGF-2, and high concentrations of insulin can activate the IGF-1R resulting in tyrosine kinase activity. Subsequently, binding or phosphorylation of cellular substrates in close proximity through SH2 binding domain leads to downstream signaling (Figure S1). The importance of IGF-1R signaling in skin development is clearly evident from a variety of studies. Transgenic mice overexpressing IGF-1 in the basal layer of skin epidermis exhibited epidermal hyperplasia, hyperkeratosis, and squamous papillomas (Bol *et al.*, 1997; Wilker *et al.*, 1999; DiGiovanni *et al.*, 2000). Conversely, IGF-1R knockout mice demonstrate severe hypoplasia (Lui *et al.*, 1993). The IGF-1R has also been shown to be important in normal epidermal differentiation (Sadagurski *et al.*, 2006) whereas other reports have identified a key role for the IGF-1R in regulating the response of cells to oxidative stress (Holzenberger *et al.*, 2003; Ikushima *et al.*, 2006). Therefore, the activation of the IGF-1R can influence all stages of epidermal homeostasis.

Experiments that assessed the role of various growth factors on the response of keratinocytes to UVB irradiation identified that the activation status of the IGF-1R was a critical component affecting UVB-induced apoptosis *in vitro* (Figure 1; Kuhn *et al.*, 1999). Inhibition of the IGF-1R, by ligand withdrawal, treatment with neutralizing antibodies, or treatment with IGF-1R-specific small molecule inhibitors before irradiation increased the sensitivity of keratinocytes to UVB-induced apoptosis (Kuhn *et al.*, 1999; Lewis *et al.*, 2006, 2008; Lewis and Spandau, 2007, 2008). For simplicity in this review, keratinocytes grown in conditions that permit the functional activation of the IGF-1R will be called (+)IGF-1R keratinocytes whereas cells containing functionally inactive IGF-1Rs will be referred to as (−)IGF-1R keratinocytes (Lewis and Spandau, 2008, Lewis *et al.*, 2008). It is important to note that the expression of the IGF-1R protein is equal in both (+)IGF-1R and (−)IGF-1R keratinocytes; they only differ in the activation status of the IGF-1R. These studies identified that the functional activation of the IGF-1R provided protection to human keratinocytes from UVB-induced apoptosis. However, an

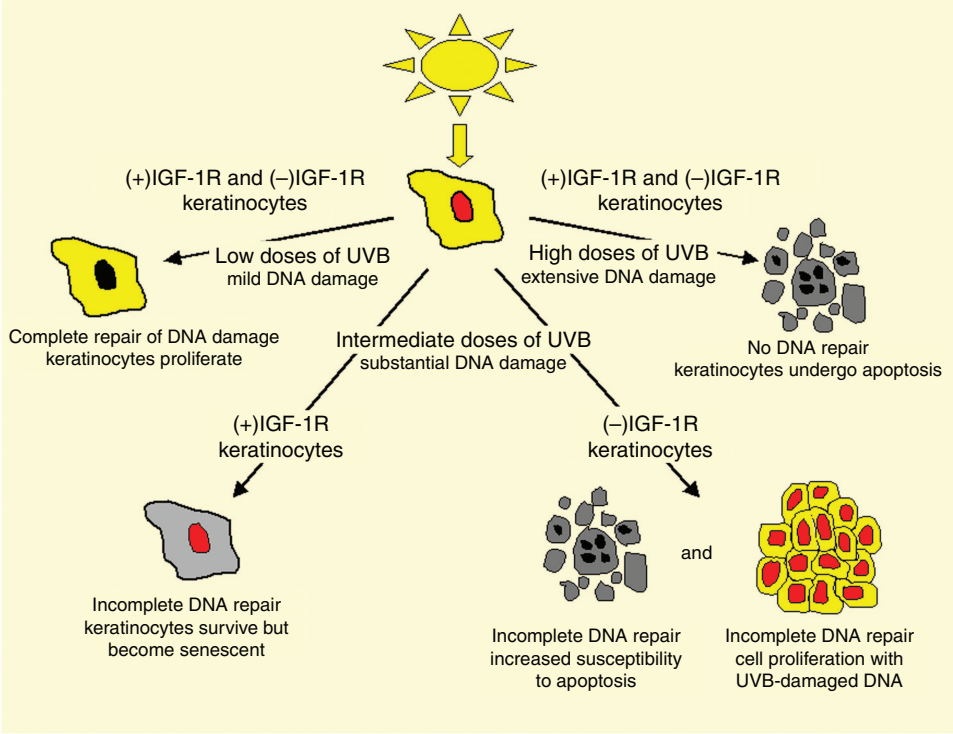

Figure 1. Keratinocyte UVB response *in vitro*. At low and high doses of UVB, the activation status of the IGF-1R does not influence the response of keratinocyte to UVB irradiation. However, at intermediate doses of UVB, the response of the keratinocytes following UVB exposure is dependent on the status of the IGF-1R. If the IGF-1R is functionally active, keratinocytes undergo stress-induced premature senescence and the unrepaired DNA damage cannot be passed to progeny. If the IGF-1R is functionally inactive during UVB irradiation, keratinocytes are more likely to undergo apoptosis; however, surviving keratinocytes continue to proliferate in the presence of UVB-damaged DNA.

equally important observation was that these surviving keratinocytes cannot replicate and become senescent (Figure 1; Kuhn *et al.*, 1999; Lewis *et al.*, 2008). We propose this UVB response occurs in the epidermis where the induction of senescence in response to UVB irradiation is a tumor evasion mechanism that maintains the important barrier function of the epidermis while ensuring keratinocytes cannot proliferate in the presence of irreparable UVB-induced DNA damaged. If the IGF-1R is functionally inactive at the time of UVB irradiation, a portion of the keratinocytes will undergo apoptosis; however, keratinocytes that survive do not become senescent, do not repair UVB-damaged DNA, and they can continue to proliferate with the potential of converting the damaged DNA into initiating carcinogenic mutations (Lewis *et al.*, 2008).

Data generated from our lab (Cotton and Spandau, 1997; Lewis *et al.*, 2008) and many others (Qin *et al.*, 2002; Chaturvedi *et al.*, 2004; Chaturvedi *et al.*, 2005) have demonstrated that UVB irradiation of keratinocytes initiates a DNA damage response involving the phosphorylation of the tumor suppressor p53. Recently, we have shown that UVB activation of p53 is also dependent on the status of the IGF-1R (Lewis *et al.*, 2008). Activation of the IGF-1R resulted in higher levels of UVB-induced total p53 protein and increased phosphorylation at serine 15 ($p53^{S15}$) and serine 46 ($p53^{S46}$) (Lewis *et al.*, 2008). Intriguingly, the phosphorylation of $p53^{S46}$ was only observed in (+)IGF-1R keratinocytes and was not influenced by UVB irradiation (Lewis *et al.*, 2008). The UVB response of keratinocytes expressing a p53 gene where serine 46 is replaced by glutamic acid ($p53^{S46D}$; which structurally and functionally mimics a phosphorylated serine residue) was found to be independent of the activation status of the IGF-1R. These data indicate that the UVB response of keratinocytes (senescence and apoptosis) requires a functional IGF-1R and the subsequent downstream phosphorylation of $p53^{S46}$.

Our *in vitro* data showing IGF-1R activation status was an important factor in the response of epidermal keratinocytes to UVB led us to hypothesize that the reduced activation of the IGF-1R may be correlated with an increased susceptibility to skin cancer *in vivo*. In a retrospective epidemiological study, we found that type 2 diabetic patients using insulin to treat their disease had a 2.5-fold decreased risk of developing NMSC over the control group and type 2 diabetic patients using non-insulin medicines to treat their disease (Chuang *et al.*, 2005). Intriguingly, the protective effect of insulin use increased with age, implying that insulin was somehow protecting against the age-associated increase in NMSC (Chuang *et al.*, 2005). These important data suggested the clinical relevance for the involvement of the IGF-1R signaling pathway in NMSC *in vivo*. Recently, we have started to examine the age-related changes in the IGF-1/IGF-1R signal transduction pathway *in vivo*. Our lab and others have shown that production of IGF-1 diminishes as fibroblasts become senescent (Ferber *et al.*, 1993; unpublished data). Given the critical role of dermal fibroblasts in supplying IGF-1 to epidermal keratinocytes, an age-related decrease in fibroblast IGF-1 may result in keratinocytes in aged epidermis having functionally deficient activation of IGF-1R and subsequently

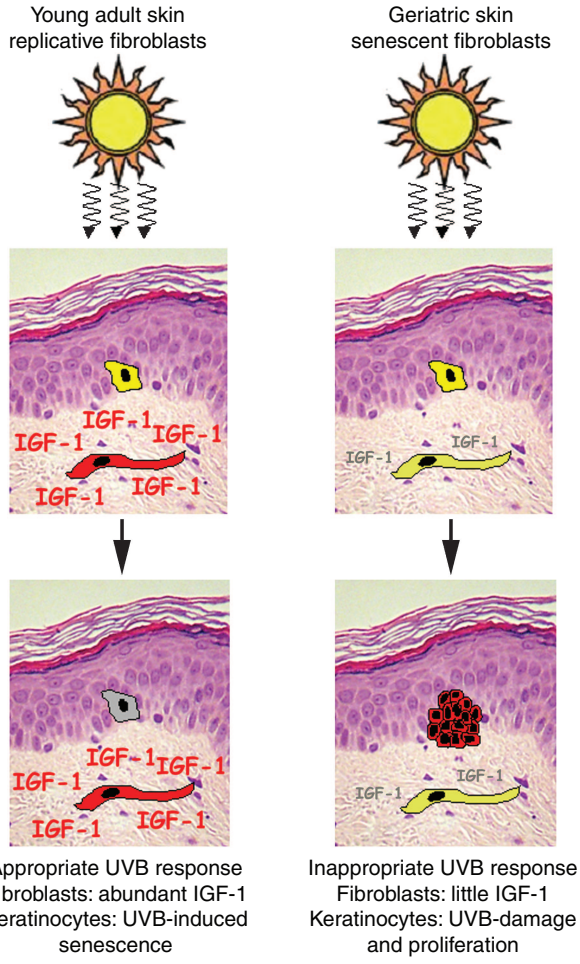

Figure 2. UVB response of the skin *in vivo*. The integration of data from our lab on the role of the IGF-1R and normal UVB response of keratinocytes (Figure 1) with our data describing the declining production of IGF-1 by senescent fibroblasts has led to the following hypothesis correlating aging skin with the development of skin cancer. Because the production of IGF-1 is silenced in aged skin, aged skin keratinocytes are provided with a reduced supply of IGF-1. Keratinocytes in aged epidermis exposed to UVB wavelengths in sunlight respond inappropriately to the UVB exposure. Instead of undergoing premature stress-induced senescence, the aged keratinocytes may continue to proliferate in the presence of UVB-damaged DNA. We believe this decrease in IGF-1 expression with advancing age is a contributor to the increase in nonmelanoma skin cancer seen in geriatric patients.

respond inappropriately to UVB irradiation. We examined the expression of IGF-1 in skin samples obtained from sun-protected anatomical locations representing young adults (20–28 years old) or geriatric individuals (>65 years old). Immunohistochemical and quantitative RT-PCR analysis of IGF-1 in samples of geriatric individuals showed a significant reduction in IGF-1 levels when compared to young adults (unpublished data). Accordingly, keratinocyte activated IGF-1R levels were high in young adult compared to virtual absence in geriatric individuals (unpublished data). It has been reported that the difference between UVB-induced DNA damage repair in young and aged human skin is the rate at which DNA damaged is cleared (Yamada *et al.*, 2006). However, we propose that any DNA damage existing while cell proliferation continues (such as we have found in aged skin) leaves the possibility for the propagation of mutations. We believe that the age-related decrease in IGF-1 expression, IGF-1R inactivation, and proliferation with DNA damage are major components in the development of NMSC seen in geriatric patients (Figure 2).

We believe that cellular senescence affects the UVB response of keratinocytes in the epidermis through two distinct and opposite mechanisms; one mechanism suppresses UVB-induced transformation of keratinocytes and the other mechanism promotes keratinocyte carcinogenesis. On the positive side, we hypothesize that keratinocytes use stress-induced senescence as a tumor evasion mechanism. The advantage to cellular senescence versus UVB-induced apoptosis is that senescence maintains the cellularity of the epidermis, thus preserving the barrier function. In other words, widespread UVB-induced keratinocyte apoptosis in the epidermis will severely compromise the epidermal barrier function whereas UVB-induced keratinocyte senescence will not. In this manner, the induction of senescence in UVB-irradiated keratinocytes suppresses carcinogenesis. On the negative side, cellular senescence in dermal fibroblasts may promote UVB-induced carcinogenesis in aging skin. We hypothesize that IGF-1 expression by dermal fibroblasts is critical for the appropriate response of keratinocytes to UVB irradiation. The silencing of IGF-1 expression by senescent fibroblasts might contribute to an increased initiation of transformed keratinocytes by UVB exposure. Furthermore, the altered inflammatory phenotype of senescent fibroblasts may promote the expansion of clones of initiated keratinocytes.

Given the increase in NMSC incidence with its associated morbidity and cost, the prevention of these tumors has significant importance. Present strategies for tumor prevention include avoiding excess UV exposure. For patients with established actinic keratoses precursor lesions, strategies include destruction by physical modalities as well as by topical chemotherapy with 5-fluorouracil or immune-mediated destruction with topical imiquimod (Gold and Nestor, 2006). Though somewhat effective in treating established pre- or low-grade cancerous lesions, these treatment strategies do not appear to effect the underlying process by which aged skin is more susceptible to neoplasia. If the major deciding feature of keratinocyte response to UVB resides in the senescence status of the dermal fibroblast, then this suggests new treatments. One possible new treatment strategy would be to develop methods to rejuvenate the fibroblasts to allow production of factors such as IGF-1. Though marketed for cosmetic purposes, skin-damaging agents ranging from chemical peels, laser resurfacing, heating of the skin, and other ''wounding'' procedures could restimulate the expression of IGF-1 in the treated fibroblasts (Meshkinpour *et al.*, 2005; DeHoratius and Dover, 2007). Since there appears to be a protective effect of exogenous insulin in skin cancer development (Chuang *et al.*, 2005), systemic treatment with IGF-1 (currently used for short-stature syndromes) could also be studied (Collett-Solberg and Misra, 2008). Thus, this new paradigm of the role of aging in the development of skin cancer could have significant clinical implications.

In summary, we propose that the reduced expression of IGF-1 that characterizes geriatric skin could be an important component in the development of aging-related non-melanoma skin cancer. Furthermore, dermal fibroblasts are critical in maintaining appropriate activation of the keratinocyte IGF-1R that can be ameliorated in aged dermis by the presence of senescent fibroblasts. Finally, this paradigm suggests a role for the IGF-1R in suppressing UVB-induced carcinogenesis by induction of stress-induced keratinocyte senescence. Further study of this model not only could allow a better understanding of carcinogenesis, it could provide the impetus for new prevention strategies.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Figure S1. IGF-1R signal transduction cascade.

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