Comment on ‘Does a History of Eczema Predict a Future Basal Cell Carcinoma?’

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TO THE EDITOR

Dyer et al. (2012) examined risk factors for basal cell carcinoma (BCC) in a relatively small cohort of veterans, who participated in the USA Veterans Affairs Topical Tretinoin Chemoprevention Trial. In addition to the usual, well-known predictors; that is, age, sun sensitivity, a history of prior BCCs, and occupational UV exposure, they found an association with a self-reported history of eczema (atopic dermatitis, AD). In their accompanying editorial, Gamba and Tang (2012) examine competing hypotheses to explain this new association. Because none of the Veterans Affairs (VA) subjects had been treated with calcineurin inhibitors or other immunosuppressives, they then speculate that either the chronic inflammation in AD or other forms of anti-inflammatory therapy for AD, such as topical glucocorticoids or UV phototherapy, could have favored the development of BCCs.

Yet, the BCCs in the VA patients did not occur in previously eczematous sites, suggesting to us that some inherent difference in the structure of the epidermis in subjects at risk for AD could explain the association of AD with an increased prevalence of BCCs. We propose two alternate epidermis-based explanations, either or both of which could be operative. First, assuming that a substantial subgroup of these VA patients have Northern European ancestry, then as many as 40–50% of the subjects with a prior history of AD could bear loss-of-function FLG mutations (Irvine et al., 2011). Proteolytic degradation of FLG, followed by either enzymatic or non-enzymatic deimination of its constituent amino acids, yields a mixture of polycarboxylic acids that includes trans-urocanic acid (t-UCA) (Scott et al., 1982), an important endogenous UV-B filter (Finlay-Jones and Hart, 1998). Reduction in the t-UCA content of stratum corneum (SC) might lead to greater UV-B penetration into the nucleated cell layers with an increased risk of malignant transformation. On the other hand, t-UCA is photo-isomerized by UV-B to cis-UCA (c-UCA), a potent, local immunosuppressive molecule (Kripke, 1984; de Fine Olivarius et al., 1998). Thus, the possibility that t-UCA deficiency, resulting from reduced FLG, could increase BCCs in this population through greater UV-B penetration must be weighed against the potential benefits of reduced c-UCA generation from t-UCA in a FLG-deficient, tumor environment.

A second, less ambiguous epidermis-based explanation could be the thinner SC that occurs in AD (Cork et al., 2009; Voegeli et al., 2009). The thinner SC in AD could result from inherited, gain-of-function mutations in kallikrein7 (KLK7; Vasilopoulos et al., 2011); loss-of-function mutations in SPINK5, which encode the KLK inhibitor, LEKTI (Sprecher et al., 2001); and/or a FLG allele-dependent increase in the pH of the SC that accompanies the barrier abnormality, even in non-inflamed, filaggrin-deficient epidermis (Gruber et al., 2011). An increase in pH inevitably would lead to activation of KLKs (Cork et al., 2009; Voegeli et al., 2009). These alterations likely converge either alone or additively to increase KLK activity and SC thinning in both lesional and non-lesional skin of AD (Elias and Schmuth, 2009). Because at least 50% of UV-B in lightly pigmented individuals is interdicted at the level of the SC (Thomson, 1955), a thinner-than-normal SC then would inevitably predispose to the development of BCCs by allowing penetration of a larger proportion of incident UV-B.

The final message should be, however, that AD is now generally acknowledged to display a prominent epidermal component, with several of its immunological sequelae occurring downstream of a flawed barrier (Elias et al., 2008). Hypotheses of causation and association with other epidermal diseases, such as BCC, should not overlook the potential role of epidermal pathology in disease pathogenesis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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REFERENCES


Abbreviations: AD, atopic dermatitis; BCC, basal cell carcinoma; c-UCA, cis-urocanic acid; KLK7, kallikrein7; SC, stratum corneum; t-UCA, trans-urocanic acid; VA, Veterans Affairs
Risk of Generalized Vitiligo Is Associated with the Common 55R-94A-247H Variant Haplotype of GZMB (Encoding Granzyme B)

TO THE EDITOR

In generalized vitiligo (GV), patches of depigmented skin and overlying hair (Picardo and Taïeb, 2010) result from autoimmune destruction of melanocytes by skin-homing autoreactive cytotoxic T lymphocytes (CTLs) (Ogg et al., 1998). In two genome-wide association studies (GWAS) to identify GV susceptibility loci in European-derived white (EUR) patients (GWAS1, GWAS2; Jin et al., 2010, 2012), we detected association with GZMB, encoding granzyme B, a serine protease marker of activated CTLs (Sattar et al., 2003). In concert with perforin, GZMB mediates direct and caspase-mediated apoptosis of target cells (Granville, 2010; Even et al., 2012), as well as proteolytic cleavage of autoantigens, creating or exposing autoimmune epitopes that may initiate or propagate the autoimmune process (Darrah and Rosen, 2010).

Meta-analysis of GWAS1, GWAS2, and replication study data for single-nucleotide polymorphisms (SNPs) genotyped in the GZMB region (Jin et al., 2012) showed greatest association with rs8192917-C (P = 5.60 × 10−8, odds ratio 1.22), a common nonsynonymous SNP (R55Q) that is in very strong linkage disequilibrium with two other common nonsynonymous SNPs, rs11539752 (P94A; P = 0.99) and rs2236338 (Y247H; P = 0.93). Together, these three variants define two predominant haplotypic multivariant GZMB polypeptide isoforms 55Q-94P-247Y (termed “QPY”) versus 55R-94A-247H (“RAH”) (McIlroy et al., 2003; Zaits et al., 2004). To carry out higher-resolution analysis of association of GV with SNPs in the GZMB region, we first imputed genotypes for all SNPs in the 1,000 Genomes Project phase 1 integrated variant call set (21 June 2012 release) across the 160-kb region (chr14:25045130–25204958) showing even nominal association with GV in the combined GWAS1 and GWAS2 dataset (Jin et al., 2010, 2012), from 101.5 kb upstream of GZMB through 55 kb downstream. After quality control procedures, there were 464 genotyped or imputed SNPs in 7,202 total subjects (Supplementary Table S1 online) owing to very strong linkage disequilibrium (Supplementary Figure S1 online). These include rs8192917 (R55Q) and rs11539752 (P94Q); none of the other seven primary associated SNPs (rs6573910, rs6573911, rs45628336, rs113822535, rs45444294, rs1126639, and rs10909625) are predicted to have functional consequences. In contrast, the associations of rs2236338 (Y247H), as well as that of another potentially functional SNP rs2273844 (stop codon within the 5′ untranslated region), were found to be secondary.

Analysis of the haplotypes defined by the three nonsynonymous SNPs rs8192917−rs11539752−rs2236338 similarly indicated that principal association with GV is with the haplotype comprising rs8192917-C−rs11539752-C. As shown in Table 2, this constitutes the higher-risk haplotype (odds ratio 1.27; P = 4.42 × 10−8), compared with the haplotype that also includes the high-risk G allele of rs2236338 (odds ratio 1.26; P = 3.26 × 10−7). Nevertheless, it is difficult to completely exclude any

Abbreviations: CTL, cytotoxic T lymphocyte; EUR, European-derived white; GV, generalized vitiligo; GWAS, genome-wide association study; GZMB, granzyme B; SNP, single-nucleotide polymorphism

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