See related article on pg 1105

COMMENTARY

New Psoriasis Susceptibility Genes: Momentum for Skin-Barrier Disruption

Eliecer Coto[1,2], Jorge Santos-Juanes[2,3], Pablo Coto-Segura[3] and Victoria Alvarez[1]

The epidermal differentiation complex gene cluster is on chromosome region 1q21.3, where the *PSORS4* locus was mapped. A common deletion of two LCE genes (*LCE3C_LCE3B-del*) was associated with psoriasis. Individuals homozygous for the deletion have an impaired response of the skin barrier to exogenous agents, facilitating the systemic skin inflammation characteristic of psoriasis.

Journal of Investigative Dermatology (2011) **131,** 1003–1005. doi:10.1038/jid.2011.14

Psoriasis is a multifactorial disease in which an individual's genetic background interacts with environmental factors to define overall risk (Griffiths and Barker, 2007). The first proof of a strong genetic component came from the high disease concordance among twins. Familial transmission studies estimated a 41% risk for the offspring of two affected parents and a 14% risk when only one parent was affected. The genetic component affects not only overall risk, but also the age of disease onset. Serological typing of human leukocyte antigen (HLA) class I antigens identified the first locus for psoriasis (*PSORS1*) in the chromosome 6p21.3 region. Further studies identified a strong association between psoriasis and the *HLA-Cw6*0602* allele (Nair *et al*., 2006). This HLA variant could play a role in the presentation of antigens to the $CD8^+$ T and natural killer cells by the epidermal cells in psoriatic lesions (Gudjonsson *et al*., 2004). Although *HLA-Cw6* remains the major genetic determinant of psoriasis, recent genome-wide association studies have identified new variants in other immunocompetent genes, such as *IL-12* and *IL-23*. These studies have contributed to our current view of psoriasis as a disease in which primary external stimuli activate the release of key cytokines by keratinocytes (Elder *et al*., 2010), initiating a cascade of molecular and cellular events that include the differentiation of naive T cells to the type 1 T-helper cells (particularly the Th1 and Th17 subsets) that infiltrate psoriatic skin.

These and other findings (e.g., the effective treatment of psoriatic patients with drugs that modulate effector lymphocytes or with antibodies against the common p40 subunit of IL-23 and IL-12) sustain the hypothesis that dysregulation of the immune response is the main primary cause of psoriasis. Factors such as abnormalities in keratinocytes and insults in the skin barrier remained secondary players. However, results from recent genetic association and functional studies have changed this scenario. In this issue of *JID*, Riveira-Muñoz *et al*. report a meta-analysis of the association between psoriasis and a common deletion (*LCE3C_LCE3B-del*) in the late-cornified envelope (LCE) cluster. This cluster is on chromosome region 1q21.3, where the *PSORS4* locus was identified. The *LCE3C_LCE3B-del* was first linked to psoriasis in a genome-wide association study on individuals of European ancestry, and the association was replicated by others (De Cid *et al*., 2009; Hüffmeier *et al*., 2010). Riveira-Muñoz *et al*. (2011) studied 9,389 psoriasis patients and 9,477 controls from populations of European ancestry (Finland, France, Germany, Ireland, Italy, Spain, the Netherlands, UK, and the United States) and of Asiatic origin (China, Mongolia, and Japan). The frequency of homozygotes for the deletion was significantly higher among the patients, with an overall odds ratio (OR) of 1.20 (95% confidence interval = 1.15–1.28) for the Europeans. This OR was much lower than the value attributed to the *Cw6* variant but was closer to the value for other well-characterized susceptibility (e.g., *IL-12* and *IL-23*) polymorphisms.

The LCE proteins are part of the epidermal differentiation complex (EDC) involved in the terminal differentiation of the epidermis (Mischke *et al*., 1996). LCE3C was expressed at a low to null level in normal skin, depending on the *LCE3C_LCE3B-del* genotype (deletion homozygotes had a complete lack of the LCE3C mRNA). In a challenging experiment, the Xavier Estivill group found a link between the deletion and an impaired skin barrier response (De Cid *et al*., 2009). Removal of the stratum corneum through adhesive tape stripping promoted the hyperproliferation and differentiation of keratinocytes and an increased expression of *LCE3C* and other genes involved in skin barrier formation. The exception was an individual homozygous for the deletion who did not show LCE3C mRNA induction (De Cid *et al*., 2009). It is well recognized that the nonlesional skin of psoriatic patients is prone to develop inflammatory lesions upon exfoliation and other mechanical stimuli (the so-called Koebner phenomenon). The obvious speculation was that the absence of intact *LCE3C* and *LCE3B* genes could lead to impaired epidermal repair after barrier disruption, making the skin more susceptible to penetration by exogenous agents. This, together with an immunological genetic background (e.g., *HLA-CW6* positivity), could facilitate the development of inflammation characteristic of psoriasis.

[1]*Genética Molecular, Hospital Universitario Central Asturias–Servicio de Salud del Principado de Asturias, Oviedo, Spain;* [2]*Department of Medicine, University of Oviedo, Oviedo, Spain and* [3]*Dermatología, Hospital Universitario Central Asturias–Servicio de Salud del Principado de Asturias, Oviedo, Spain*

Correspondence: Eliecer Coto, Genética Molecular–Hospital Central Asturias, C. Villamil 33006 Oviedo, Spain. E-mail address: eliecer.coto@sespa.princast.es

Clinical Implications

- Recent studies of immunologic contributions to psoriasis are now complimented by genetic association studies that implicate structural proteins in keratinocytes, as well.
- Riveira-Muñoz *et al*. report a meta-analysis of the association between psoriasis and a common deletion in the late-cornified envelope cluster, potentially leading to dimished barrier function.
- These findings may explain why unaffected skin in patients with psoriasis becomes affected relatively easily after externally generated inflammation or trauma. They may also offer new therapeutic opportunities.

The *LCE-del* would compromise the skin barrier through a loss of function. There is a recent example of how a genetically improved EDC function could also promote inflammation, facilitating the development of psoriasis. The S100 calcium-binding proteins are encoded by genes in the *PSORS4* cluster, approximately 500 Mb from the LCE cluster (Jackson *et al*., 2005). Like LCE proteins, the S100 proteins are components of the cornified envelopes and skin barrier. However, human S100A7 and S100A15 proteins also act as chemokines upregulated and released during skin inflammation. Their proinflammatory effects are mediated through its binding to receptors of advanced glycation end products on leukocytes. In mice, the overexpression of S100a7/a15 resulted in skin prone to inflammation, a phenomenon that resembles the histological and molecular characteristics of nonlesional psoriatic skin (Wolf *et al*., 2010). These mice were also more likely to develop skin lesions in response to proinflammatory stimuli such as skin irritants and, interestingly, exfoliation of epidermis by tape stripping.

Riveira-Muñoz *et al*. (2011) observed a significant negative correlation between the frequency of *LCE3C_LCE3B-del* among controls and the corresponding OR for psoriasis: the more common the risk allele, the smaller its effect on psoriasis risk. In Europe, this seems to follow a north–south gradient. In our population (Asturias, northern Spain), the frequencies of deletion homozygotes in controls (n = 400) and psoriasis patients (n = 320) were 42 and 36%, respectively, with an OR of 1.30 (Coto *et al*., 2010). These values fit well in the frequency-risk correlation model of Riveira-Muñoz *et al*. (2011). Although sampling error cannot be excluded, a genuine effect of this phenomenon on the genetic predisposition to psoriasis is possible and requires further investigation. The *LCE3C_LCE3B-del* is a functional gene variant, and it is probably responsible for the observed risk. However, a nearby functional variant in linkage disequilibrium (LD) with the deletion could also contribute to the risk of developing psoriasis. For instance, the *LCE-del* could be in LD with a variant that increased the expression of *S100* genes; in such a case, individuals homozygous for the *LCE-del* and with increased S100 expression might be at the highest risk for psoriasis. Differences in haplotype frequencies among populations could thus explain the different OR values for the *LCE-del*. An interaction between the *LCE-del* and an environmental factor that had a south–north gradient could also explain the correlation between the deletion frequency and risk.

These studies will fuel new research on other *PSORS4* genes. The EDC cluster contains more than 50 genes from several families. The *LCE3C_LCE3B-del* is only one of the many variants that could affect the expression or function of these components. Association studies with single-nucleotide polymorphisms (SNPs) within this region will be necessary to identify other risk alleles. At least one SNP that mapped to this cluster (rs4112788) has been linked to psoriasis, but the risk allele was in almost complete LD with the *LCE-del* and would thus be a surrogate marker for the deletion (De Cid *et al*., 2009; Zhang *et al*., 2009). The resequencing of this genome region in psoriasis patients and healthy controls is necessary to identify whether other common and rare variants contribute to the risk for psoriasis. Other *LCE* and the *S100A7* and *S100A15* genes are the strongest candidates with which to start this search.

Finally, exposure to UV radiation is usually beneficial in psoriasis, but a subset of patients develop severely photosensitive psoriasis (Rutter *et al*., 2009). In these patients, UV radiation induces thickening of the stratum corneum, an effect mediated by the upregulation of *LCE* and other EDC genes (Jackson *et al*., 2005). Could the *LCE-del* and other EDC gene variants modify the extent of skin's response to UV irradiation in psoriasis? A positive answer might have clinical consequences, because the genotyping of these variants could help identify patients likely to respond adversely.

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES

Coto E, Santos-Juanes J, Coto-Segura P *et al*. (2010) Mutation analysis of the LCE3B/LCE3C genes in psoriasis. *BMC Med Genet* 11:45

De Cid R, Riveira-Muñoz E, Zeeuwen PL *et al*. (2009) Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. *Nat Genet* 41:211–5

Elder JT, Bruce AT, Gudjonsson JE *et al*. (2010) Molecular dissection of psoriasis: integrating genetics and biology. *J Invest Dermatol* 130:1213–26

Griffiths CE, Barker JN (2007) Pathogenesis and clinical features of psoriasis. *Lancet* 370: 263–71

Gudjonsson JE, Johnston A, Sigmundsdottir H *et al*. (2004) Immunopathogenic mechanisms in psoriasis. *Clin Exp Immunol* 135:1–8

Hüffmeier U, Bergboer JG, Becker T *et al*. (2010) Replication of LCE3C-LCE3B CNV as a risk factor for psoriasis and analysis of interaction with other genetic risk factors. *J Invest Dermatol* 130:979–84

Jackson B, Tilli CM, Hardman MJ *et al*. (2005) Late cornified envelope family in differentiating epithelia—response to calcium and ultraviolet irradiation. *J Invest Dermatol* 124:1062–70

Mischke D, Korge BP, Marenholz I *et al*. (1996) Genes encoding structural proteins of epidermal cornification and S100 calcium-binding proteins form a gene complex ("epidermal differentiation complex") on human chromosome 1q21. *J Invest Dermatol* 106:989–92

Nair RP, Stuart PE, Nistor I *et al*. (2006) Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet* 78:827–51

Riveira-Muñoz E, He S-M, Escaramís G *et al*. (2011) Meta-analysis confirms the *LCE3C_LCE3B* deletion as a risk factor for psoriasis in several ethnic groups and finds interaction with *HLA-Cw6*. *J Invest Dermatol* 131:1105–1109

Rutter KJ, Watson RE, Cotterell LF *et al*. (2009) Severely photosensitive psoriasis: a phenotypically defined patient subset. *J Invest Dermatol* 29:2861–7

Wolf R, Mascia F, Dharamsi A *et al*. (2010) Gene from a psoriasis susceptibility locus primes the skin for inflammation. *Sci Transl Med* 2: 61ra90

Zhang XJ, Huang W, Yang S *et al*. (2009) Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. *Nat Genet* 41:205–10

See related article on pg 1139

Oxidatively Generated Damage to DNA by UVA Radiation in Cells and Human Skin

Jean Cadet[1] and Thierry Douki[1]

Exposure of cells and human skin to UVA radiation oxidatively induces damage to DNA that consists mostly of 8-oxo-7,8-dihydroguanine (8-oxoGua), together with relatively minor amounts of oxidized pyrimidine bases and oligonucleotide strand breaks. Singlet oxygen generated by the type II photosensitization mechanism forms 8-oxoGua, with a small contribution by hydroxyl radicals. The mechanisms of UVA-mediated formation of DNA oxidation products indicate the absence of induction of double-strand breaks.

Journal of Investigative Dermatology (2011) **131**, 1005–1007. doi:10.1038/jid.2011.51

It is well documented that, in contrast to UVB radiation, the less energetic UVA photons exert most of their biological effects on cells and skin in an oxygen-dependent manner and on a broad range of cellular targets, including membranes, proteins, and DNA. UVA radiation is now recognized as a class I carcinogen (El Ghissassi *et al*., 2009) and is suspected to play a significant role in the induction of melanoma (although recently questioned in the case of the Xiphophorus hybrid fish model by Mitchell *et al*., 2010). Numerous attempts have been made over the past two decades to delineate the molecular effects of UVA radiation on cellular DNA, with an emphasis on the putative role of reactive oxygen species (ROS), which are generated mostly by endogenous photosensitizers, according to their so-called "photodynamic effects" (Cadet *et al*., 2005).

UVA is able to induce 8-oxo-7,8-dihydroguanine and, to a lesser extent, oxidized pyrimidine bases and DNA single-strand breaks

The main DNA oxidation product of UVA radiation has been identified in several types of isolated cells (for a recent review, see Cadet *et al*., 2009) and human skin (Mouret *et al*., 2006) as 8-oxo-7,8-dihydroguanine (8-oxoGua). This ubiquitous DNA oxidation product, which may be produced by hydroxyl radical (•OH), singlet oxygen ($^1O_2$), one-electron oxidants, or peroxynitrite, is widely used as an exposure biomarker of oxidative stress on cellular DNA (Cadet *et al*., 2008). Putative endogenous photosensitizers (which include quinones, porphyrins, and flavins) may act through one-electron (or hydrogen atom) abstraction (type I mechanism) and/or triplet energy transfer to molecular oxygen with subsequent formation of $^1O_2$ (type II mechanism). Insights into the mechanism(s) involved in the UVA-mediated formation of 8-oxoGua were gained from enzymatic-based experiments and high-performance liquid chromatography associated with electrochemical detection and high-performance liquid chromatography–electrospray–tandem mass spectrometry (Cadet *et al*., 2009).

Incubation of DNA released from isolated cells with bacterial endonuclease III (Endo III) and formamidopyrimidine glycosylase (Fpg), two DNA repair enzymes, allowed conversion of oxidized pyrimidine and purine bases, respectively, into single-strand breaks (SSBs), detected and quantified by either the alkaline comet assay or the alkaline elution technique (Kielbassa *et al*., 1997; Pouget *et al*., 2000). Exposure of human monocytes to UVA radiation gave rise to the predominant formation of Fpg-sensitive sites, mostly 8-oxodGuo and 2,6-diamino-5-hydroxy-4-formamidopyrimidine. The global yield was 6.1-fold higher than that of oxidized pyrimidine bases and 2.1 times higher than that of non-enzymatic DNA nicks (which may consist of SSBs, double-strand breaks (DSBs), and alkali-labile sites) (Pouget *et al*., 2000). These ratios must be compared with those determined for human monocytes exposed to the gamma rays of ^{60}Co, which are significantly lower owing to the relative yields of Fpg-sensitive sites with respect to strand breaks and oxidized pyrimidine bases (0.37 and 0.91, respectively). In the latter case, the predominant indirect effects of ionizing radiation responsible for most of the DNA damage (Douki *et al*., 2006) are rationalized in terms of major implication of •OH. Under these oxidation conditions, similar levels of pyrimidine and purine base lesions are formed whereas the number of SSBs increases. DSBs are also generated upon exposure to ionizing

[1]*Laboratoire "Lésions de Acides Nucléiques," SCIB-UMR-E no. 3 (CEA/UJF), FRE CNRS 3200, Département de Recherche Fondamentale sur la Matière Condensée, Grenoble, France*

Correspondence: Jean Cadet, Institut Nanosciences et Cryogénie/Direction de Sciences de la Matière, CEA/Grenoble, F-38054 Grenoble Cedex 9, France. E-mail: jean.cadet@cea.fr