Alain Taïeb
National Reference Centre for Rare Skin Disorders, Department of Dermatology and Pediatric Dermatology, Inserm U876 University Victor Segalen Bordeaux 2, France
Tel.: +33 556 794 705
Fax: Fax
alain.taieb@chu-bordeaux.fr

Molecular genetics of the epidermal differentiation complex: perspectives for dermatology and medicine or the 'purloined letter syndrome'

'Over the last 20 years, a considerable amount of information has been collected on monogenetic skin disorders, indicating clearly that local factors are the unique determinants of the local expression of disease'.

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A durable paradox: the skin, so close but also so remote from dominant medical thinking

Compared with other organs the skin is immediately accessible and valued for providing diagnostic clues in systemic disorders. The term biopsy was coined by Besnier, a dermatologist, at the end of the 19th century and its use was championed by Darier, the founder of dermatopathology, in the early 20th century [1]. Data collected at the live tissue level in dermatology have, thus, been more considerable than in any other medical specialty. However, a limited therapeutic armamentarium is available in dermatology compared with other disciplines. Why is this the case? One speculation is that besides economic or market considerations, which are important to drive drug development, limitations raised to investigate the mechanism of skin disorders and, thus, provide new treatments, were more intellectual than practical. They are of the same kind as those operating in Edgar Allan Poe's famous short story 'The Purloined Letter' (1844), in which the closest evidence is dismissed for complex speculations. The most common chronic skin diseases, such as non-occupational eczema (atopic dermatitis [AD]), psoriasis or vitiligo, have been (and still are in major textbooks) explained conveniently as reflecting disturbances situated primarily outside the skin. Since the discovery of immunology and allergy, the immune system has been a favorite in medical thinking applied to skin disorders, on top of more vague digestive, liver or endocrine disturbances, to cite a few. Allergic, autoimmune or more recently autoinflammatory mechanisms, as a result of heritable predispositions altering the immune system (innate or adaptive) that fit the older concept of diathesis, have been central to the understanding of chronic skin disorders [2]. The skin remained a mere target, offering little interest to be investigated locally except for dissecting the effector arm of pathomechanisms. Among other arguments, a strong case was made in favor of this view from evidence that systemic drugs, especially corticosteroids but primarily immunosuppressants,

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such as cyclosporine, work in psoriasis and AD [3] but vitiligo, overall, is poorly responsive to systemic drugs. However, over the last 20 years, a considerable amount of information has been collected on monogenetic skin disorders, indicating clearly that local factors, such as mutations in structural proteins or enzymes expressed in the epidermis, are the unique determinants of the local expression of disease [4].

Filaggrin mutants in AD: a Copernician revolution in the so-called 'allergic disorders'

The links of ichthyosis vulgaris (IV) and AD, which have been characterized recently at the molecular level [5], highlight that skin itself is a good angle of attack when looking at the pathophysiology of chronic skin diseases. AD is a good model to illustrate the conceptual representations linking skin disorders and internal medicine in a humoralist perspective. In particular, the visible oozing of eczema and alternating phases of AD and wheezing gave credit to the role assigned to cutaneous symptoms by the Hippocratic school. This doctrine, which limits therapeutic intervention to a minimalist approach, is still unconsciously prevalent in dermatological treatment since major concerns have been raised against the use of topical corticosteroids and, more recently, against topical calcineurin inhibitors, such as tacrolimus and pimecrolimus [6]. However, in the last few decades, several authors have pointed out that atopy in AD might be a secondary process, rather than the cause of the disease [7–9]. Together with the confirmation of this view in animal models, such as the NC/Nga mouse [10], the identification of genes predisposing to an impaired barrier function of the epidermis intensified after the discovery of the linkage of genes encoding proteins involved in the epidermal differentiation complex (EDC) situated on chromosome 1 with the chronic skin disorders AD and psoriasis [11]. In 1999, based on a series of clinical and experimental arguments, I suggested that for prevention purposes we should focus our attention directly on the skin as a primary step in the initiation of AD and atopic disorders, highlighting that looking at filaggrin (FLG), which was known to be defective in IV, was an excellent candidate gene approach [8]. I also mentioned that "the distinction of this phenotype (IV) from AD is so blurred that the rate of association might be higher (than 4%)". Molecular studies have now demonstrated that FLG mutants may represent more than 40% of patients in some European hospital-based cohorts of AD [5], other mutations of the FLG gene probably being responsible for the phenotype in non-European descent populations (IRVINE A, PERS. COMM.). I also indicated another argument not yet addressed in this disorder: "the degradation of filaggrin leads to urocanid acid, a molecule, which may serve as an immunomodulator in the epidermis, providing a link between a structural protein basis and immune pathomechanisms *in situ*" [12]. This aspect (interactions between nonimmune and immune aspects of AD and atopic disorders) should now be investigated in more depth in a therapeutic perspective, based on the large body of knowledge accumulated over a few years. Since a large number of IV patients (at least 10% of the European-descent populations are carriers of loss-of-function FLG mutants, which are heritable in a semidominant fashion according to genotype–phenotype analysis) do not develop AD or asthma, a limiting factor is probably at work in this subgroup, which needs to be studied for constitutional downregulation of atopic pathways. Indeed, the link between the barrier anomalies and the innate immune system are now at the center of the pathogenesis of AD [13]. One of the most intriguing challenges in the puzzle of atopic diseases is now to understand the proven link between skin barrier impairment and asthma/rhinitis, which occurs in the context of AD in carriers of FLG loss-of-function mutations [5]. I suggested in the 1999 paper that "the usual clinical course (of AD), with improvement in the second year of life, could be due to improved epidermal differentiation due to normal postnatal maturation, leading to a parallel decrease in prevalence of positivity on aeroallergen patch testing. However, memory cutaneous T cells remaining in the skin-homing compartment could be stimulated once more if the allergen could reach this compartment via the skin again (if irritated and more 'leaky') or via the mucosal route and the blood (inhaled and ingested allergens for cross-reacting antigens). The common shift towards respiratory manifestations may be linked either to the recirculation of such homing T cells, which may lose their homing-site-specific receptors under some environmental conditions, as they (can) do *in vitro*, or to the consequences of common viral respiratory illnesses, which favor the entry of aeroallergens via the respiratory epithelium" [8]. This overall scenario appears still tenable in 2007 and suggests, now more strongly than before, that preventing the early steps of development of AD in at-risk individuals by an adapted corneotherapy. This concept, proposed by Albert Kligman [14], could be implemented in a near future as a gene or gene-product therapy local delivery system to limit part of the asthma epidemic [8]. Genotyping at birth for the common FLG mutants may help in decision-making for this kind of prevention if this concept holds true.

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EDC molecular genetics & speculations for the benefits of being predisposed to atopy

When I reconsider the following sentences written in my 1999 hypothesis in the context of recent data, dry skin was not what I speculated as being a primary selective advantage but rather the type of immune response: "atopy, when defined as a genetic trait predisposing to privilege T helper (Th)2 responses to common environmental allergens, also designated as atopens, can be considered as a latent trait in a substantial proportion of the population. The size of this population is yet to be determined, since most epidemiologic studies indicate constant progression of the epidemic. It is probably dependent on several genes, some of which have already been studied by molecular epidemiologists

and linked to immunoglobulin (Ig)E regulatory pathways. This trait is probably associated, due to its prevalence, with some unknown benefit to carriers". Knowing now that the bulk of the predisposition for AD in the European population is in FLG mutants (and probably in other EDC protein mutants yet to be found) it is now possible to consider that 10% of the population have evolved into a skin phenotype, which has predisposed a subset of them to mount a skin-hosted IgE response, thus, rendering them more competitive for survival. It is possible that owing to various environmental factors, the burden of xerosis and superimposed AD had a moderate impact in our ancestors. The old parasite theory, which has been a precursor of the more recent hygiene theory [15], considered that having efficient responses to intestinal worm infections through high IgE production was beneficial for humans and had become subsequently subverted into aberrant 'atopic' responses to common environmental antigens. I would today propose the alternative cutaneous-based hypothesis: getting rid of skin parasitic infections more easily was a selective advantage for FLG mutants in the past in the sense that it could have provided improved access to sexual reproduction. This, of course, has to be proven but appears testable for scabies, the remaining large-scale prevalence corneoparasitic skin disease.

Conclusion

Returning to what could be called the 'purloined letter syndrome' in dermatology, the future in our discipline looks very exciting. Following the heuristic approach made in AD, we know that the respective role of skin and non-skin factors in chronic skin disorders can now be better explored when an angle of attack is found in the skin itself. Progress made in the understanding of AD will probably precede similar breakthroughs in psoriasis and, hopefully, vitiligo [16]. We should certainly think differently regarding skin disorders in the context of general medicine. A true Copernician revolution is now operating in the field of chronic skin disorders, which have evolved from a status of epiphenomenona revelators of internal predisposing traits to become true diseases of the skin.

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Affiliation

- *Alain Taïeb, Deg*
  Professor, National Reference Centre for Rare Skin Disorders, Department of Dermatology and Pediatric Dermatology, Inserm U876 University Victor Segalen Bordeaux 2,
  and,
  Bordeaux University Hospitals, France
  Tel.: +33 556 794 705
  Fax: Fax
  alain.taieb@chu-bordeaux.fr