Progress in Molecular Dermatology

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Heritable skin diseases manifest with a spectrum of conditions with variable cutaneous involvement. At one end of the spectrum, the clinical findings may be limited to the skin, hair, and nails, while at the other end of the spectrum the cutaneous manifestations can cause considerable morbidity and mortality. Many of the genodermatoses have continued to pose a clinical challenge to the practicing dermatologist, in part because of their rarity, and in part because of the complexity of the phenotypic manifestations. This diagnostic dilemma has been compounded by the complexity of the traditional classifications, often riddled with eponyms. Furthermore, many of these conditions have not been well defined at histopathological and/or ultrastructural level, and the understanding of the molecular basis has been incomplete.

With the advent of molecular biology in general and with the near completion of the human genome project, there has been tremendous progress towards understanding the molecular basis of various genodermatoses. In fact, there are currently at least 80 distinct genes that harbor mutations that explain the phenotypic manifestations characteristic of such heritable skin diseases (1). Examination of the mutation database has revealed a number of conditions where the candidate genes could have been predictable on the basis of clinical manifestations and histopathological and/or ultrastructural findings. An example of such conditions is epidermolysis bullosa (EB), which manifests with blisters and erosions as a result of dermal-epidermal separation due to fragility of the skin. It was hypothesized that the structural basement membrane zone (BMZ) genes could serve as candidate genes for mutations in EB, and this hypothesis is now proven correct by demonstration of mutations in 10 distinct genes encoding the structural proteins of the cutaneous BMZ (2). Similarly, the Ehlers-Danlos syndrome, a condition known to manifest with compromised integrity of the collagen fiber meshwork in a variety of tissues, including the skin, was thought to result from mutations in the genes encoding genetically distinct collagens or enzymes participating in their post-translational modification, and this postulate has also been proven correct by demonstration of a number of mutations in various extracellular matrix genes.

In contrast to the obvious candidate genes, elucidation of the molecular basis of various genodermatoses has yielded a number of surprises. An example is Vohwinkel’s syndrome, which originally was shown to result from mutations in the gene encoding loricrin, an epidermal envelope protein. Subsequently, however, analysis of families with the classic forms of Vohwinkel’s syndrome, manifesting with keratoderma with hereditary deafness, revealed mutations in the GJB2 gene which encodes connexin-26, a cell-cell communication protein. Furthermore, Hailey-Hailey disease and Darier’s disease have been shown to result from mutations in ATP-dependent calcium transporter genes, ATP2C1 and ATP2A2, respectively. Another surprising gene/protein system relates to the demonstration of mutations in the ABCG6 gene underlying pseudo-xanthoma elasticum, a disease affecting the elastic structures in the skin, the eyes, and the cardiovascular system. Quite unexpectedly, this gene is expressed predominantly, if not exclusively, in the kidney and the liver, and the PXE should probably be considered as a metabolic disorder with secondary involvement of the extracellular matrix of connective tissue.

Elucidation of the molecular basis in various genodermatoses has greatly impacted on our understanding of the phenotypic variability of these conditions and associated features. An example of improved understanding of the phenotype/genotype correlations is provided by a paper in this issue by Virtanen et al. (3). These authors have examined a cohort of 13 patients with epidermolytic hyperkeratosis (EHK) which is sometimes associated with palmoplantar keratoderma (PPKD). The authors were able to identify distinct mutations in the KRT1 and KRT10 genes which are known to underlie this particular group of epidermal keratinization disorders. Importantly, however, examination of the mutation database revealed that KRT1 mutations were invariably associated with keratoderma while only one out of seven patients with KRT10 mutations had PPKD. Interestingly, the patients with KRT10 mutations responded well to oral or topical retinoid treatment while those cases with KRT1 mutations were less responsive. Thus, genotypic analysis of the patients, with respect to mutated genes, could potentially be used as a prognostic marker to predict the efficacy of retinoid treatment of patients with EHK and would provide an explanation to non-responsiveness in certain patients.

Another paper in this issue by Weber et al. (4) reports on the development of squamous cell carcinoma (SCC) in four patients with epidermolytic bullosa (EB). Specifically, three patients suffering from the most severe, recessive dystrophic EB (RDEB) were shown to have SCC, a known association with very poor prognosis, as most of the patients die from aggressively metastasizing SCC within five years of the diagnosis of the first malignant lesion. Interestingly, these authors were able to diagnose SCC also in one patient with generalized atrophic benign EB, a milder condition known to result from mutations in the 180-kD bullous pemphigoid antigen/type XVII collagen gene (BPAG2/COL17A1). The authors point out that SCC in this condition is very infrequent and appears to have a better outcome than SCC in RDEB. The mechanisms for development of cutaneous malignancy in EB are currently unknown, but its poor prognosis in RDEB emphasizes the importance of studying this rare, yet clinically devastating association.

One of the future areas of research on heritable skin diseases relates to attempts to develop gene therapy for these complex
conditions. Although skin is potentially an ideal target organ for development of gene therapy due to its accessibility and our ability to propagate skin cells, such as keratinocytes and fibroblasts, in culture, several technical difficulties have hampered the implementation of cutaneous gene therapy as of today. The potential problems of cutaneous gene therapy relate to the relatively low efficiencies of the gene therapy approaches in general, and the mechanisms of delivery to the skin in particular. A forthcoming symposium, the Berzelius Symposium on Cutaneous Gene Therapy, which will be organized in September in Uppsala in connection with the annual meeting of the European Society for Dermatological Research in Stockholm, will canvas the field from various theoretical and technical vantage points. This important meeting will undoubtedly facilitate our development of gene therapy approaches applicable to skin disorders in the future. The abstracts of this meeting are published in this issue of Acta Dermato-Venereologica. We encourage all readers carefully examine the Symposium abstracts in the hopes that it will be helpful in our combined efforts to develop effective treatments for this group of devastating skin diseases.

REFERENCES