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Secondary Modifiers and the Phenotypic Variability of Junctional Epidermolysis Bullosa

In this issue Professor Dédée Murrell, Sydney, Australia, and collaborators (Dang et al. p. 438–448) report on phenotypic variability in junctional epidermolysis bullosa with pyloric atresia (JEB-PA). They conclude that environmental factors and genetic modifiers must contribute to the clinical manifestations of this disease, which is caused by mutations in the *ITGB4* gene.

JEB-PA is an autosomal recessive blistering skin disorder that includes lethal and non-lethal variants. The reasons for variable severity have remained elusive, since all patients seem to have mutations in the integrin alpha 6 or integrin beta 4 genes, *ITGA6* and *ITGB4*. In this study, three families were analysed and their *ITGB4* mutations identified. One family was particularly interesting, since it had one sibling with and another without pyloric atresia (PA), both with the same homozygous *ITGB4* mutation. The study carefully compares clinical phenotypes using immunofluorescence mapping and ultra-structural analysis of skin biopsies. The observations extend our knowledge on the integrin mutations and help evaluate the genotype/phenotype correlations in JEB-PA. It becomes evident that environmental, epigenetic or other genetic modifying factors must play a role in this form of epidermolysis bullosa (EB), since the clinical variability cannot be explained alone on the basis of the mutated integrin beta 4 subunit.

Interestingly, a recent paper (1) described a genetic modifier for another EB type, dystrophic EB (DEB). In this case, a polymorphism in the gene for matrix metalloproteinase-1 (MMP-1) seems to influence the presence of collagen VII protein, the major anchoring fibril component, in the skin of patients with DEB. The polymorphism leads to increased MMP-1 activity, which in turn, degrades normal and mutated collagen VII in the skin. Patients with recessive DEB, who already have reduced amounts of mutated collagen VII in the skin, are particularly sensitive to this additional modulation. The presence of the polymorphism and, thus, more active MMP-1, leads to loss of anchoring fibril function and worsens the dysadhesion in the skin. Subsequently, skin blistering and scarring are enhanced, and the clinical phenotypes become more severe.

In analogy to this, the present paper by Dang et al. suggests that secondary modifiers also determine the development of pyloric atresia in conjunction with *ITGB4* mutations. It will be exciting to discover the identity of such genetic modifiers.

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Penetration Pushes Pigmentation in Vitiligo: Calcineurin Inhibitors Under Occlusion

Therapeutic options in vitiligo include photochemotherapy, ultraviolet B (UVB) therapy, systemic steroids, or, as more recent studies have proposed, vitamin D_3-analogs, excimer laser or topical calcineurin inhibitors (1). Meta-analysis of controlled studies has revealed that there is no one therapeutic option that could be considered the gold standard in vitiligo. Therapeutic efficacy depends rather on the type of vitiligo, areas of involvement, and duration of disease (1).

In this issue Hartmann et al. (p. 474–479) publish their study investigating 30 patients with vitiligo. The authors report that treatment of vitiligo with the topical calcineurin inhibitor tacrolimus 0.1% is also effective in longstanding vitiligo. Moreover, not only does tacrolimus 0.1% effectively treat vitiligo of the face and neck, as published previously (81% response), but therapeutic efficacy of tacrolimus 0.1% in vitiligo was also achieved in other skin areas, such as the arms, by using overnight occlusion therapy (80% response) (1). However, and confirming previous studies, acral skin also remained unresponsive to this type of treatment.

Calcineurin inhibitors are believed mainly to inhibit T-cell function by specifically blocking calcineurin. Activated calcineurin normally allows nuclear factor of activated T cells-mediated gene transcription to induce the expression of T-cell cytokines and many other T-cell activation-induced proteins. Therefore, suppression of auto-aggressive T cells is considered the main mode of action of calcineurin inhibitors in vitiligo. However, recent work has emphasized that tacrolimus may directly enhance the proliferation of both melanocytes and melanoblasts, and the present study also states that pa-

tients with darker skin responded better (2). As occlusive application is thought to regulate penetration of an active compound into the skin, the present study indicates that penetration pushes pigmentation in vitiligo when treated with calcineurin inhibitors. This effect may be mediated both by blocking T-cell activation and by direct promotion of pigmentation, which should start at the site of the hair follicles. Thus, skin penetration of calcineurin inhibitors determines therapeutic efficacy in vitiligo.

Treatment of atopic dermatitis with topical application of calcineurin inhibitors has been studied in depth, and is now a well-accepted therapeutic option. Other indications are being investigated, and among them there is good evidence that calcineurin inhibitors are also effective in diseases such as flexural psoriasis, seborrhoeic and contact dermatitis, lichen sclerosus, lichen planus, erosive oral lichen planus, and, last but not least, vitiligo of the face and neck (3–5). One major concern when applying topical calcineurin inhibitors, especially under occlusive treatment, is elevation of blood levels with systemic immune suppression. Importantly, in the present study with limited parts of the body being treated, there was no significant elevation in tacrolimus blood levels. Thus, in conclusion, only occlusive application of tacrolimus may allow effective treatment of vitiligo in some areas that are otherwise unresponsive to this treatment option. Further studies are needed to assess the blood levels of tacrolimus and its long-term effects when larger areas are treated under occlusion.

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