New Era for Skin Fragility Therapy

Two papers in this issue highlight gene therapy for skin fragility diseases. March and colleagues employed the transcription activator-like effector nuclease to disrupt dominant-negative epidermolysis—causing mutations in keratin 10 (KRT10) alleles in keratinocytes, showing abrogation of disease phenotypes in a murine model. Takashima and colleagues employed a different nuclease system, CRISPR/Cas9, to co-opt non-homologous end-joining to correct a common frameshift mutation in one of the alleles of the collagen type VII (COL7A1) gene, restoring COL7A1 expression in recessive dystrophic epidermolysis bullosa fibroblast cell lines and COL7A1 function and distribution in vivo. Both of these programmable nucleases may offer feasible and safe ex vivo somatic cell-based gene therapy for skin fragility diseases. See page 1634.

Bacterial Lipoteichoic Acid Evokes Inflammation and Damages Skin Barrier

Brauweiler and colleagues investigated the effects of lipoteichoic acid (LTA), a cell wall product from Staphylococcus aureus, which induces significant infection via penetration of the skin barrier and triggering an innate response. LTA induced expression of inflammatory cytokines, including IL-1 and chemokines, caused epidermal thickening and hyperproliferation. LTA injection also recruited neutrophils to the site of injection, resulting in damage to the skin barrier and reduction of the barrier proteins filaggrin and loricrin. Treatment with an IL-1 receptor antagonist prevented neutrophil recruitment and consequent loss of filaggrin and loricrin. Thus, S. aureus LTA induces skin features reminiscent of atopic dermatitis via IL-1-mediated inflammation and resultant skin barrier damage. See page 1753.

Evolution of a Recurrent Epidermotropic Metastatic Melanoma

During melanoma evolution, BRAFV600E or NRAS mutations in precursor lesions are thought to precede accumulation of additional activating mutations in TERT or inactivating mutations in CDKN2A or PTEN, resulting in melanoma, followed by genomic instability, yielding metastatic potential. Davidson and colleagues used whole-exome sequencing to probe the dynamic evolution of an atypical case of recurrent epidermotropic metastatic melanoma. Although no BRAFV600E or NRAS mutations were identified, driver mutations in MAP2K1 and an inversion leading to AKAP9-BRAF fusion were uncovered. Tumor evolution involved counterselection of subclones with greater numbers of mutations and neoantigen burden in favor of emergence of subclones with lower neoantigen burden. See page 1769.

Racial Differences Contribute to Psoriasis Treatment Disparities

Although biologics are efficacious treatment options, most patients with psoriasis do not receive them. Many patients receive only topical treatments or no treatment at all, and undertreatment disproportionately affects minorities and other disadvantaged individuals. In a free-listing study of 68 biologic-naïve patients with psoriasis, Takeshita and colleagues found that black patients were more commonly “unfamiliar” with biologic therapies compared with white patients. The authors concluded that this unfamiliarity may contribute to differences in psoriasis treatments between black and white patients unrelated to other socioeconomic factors and that such variations may stem from differences in exposure or understanding of the treatments. See page 1672.

Uncovering the Pathogenesis of DRESS

Severe cutaneous adverse drug reaction with eosinophilia and systemic symptoms (DRESS) commonly affects the liver and involves effector T cells and allergic skin inflammation. However, its pathogenesis remains unclear. Tsai and colleagues reported that type II innate lymphoid cells (ILC2s) were increased at the acute stage of DRESS. The ILC2s produced T helper type 2 cytokines and stimulated eosinophils, as well as levels of the IL-33 receptor serum soluble ST2, IL-5, and TSLP. After steroid treatment, patient symptoms improved and mediator levels decreased; however, IL-33, sST2, IL-5, and TSLP levels were increased in slow responders. These findings implicate ILC2s and the IL-33/ST2 axis in DRESS pathogenesis and suggest that soluble ST2 may be a useful biomarker for DRESS liver involvement. See page 1722.