Recombinant Correction

Mutations in the filaggrin (FLG) gene underlie the epidermal barrier defects of ichthyosis vulgaris and are features of the murine “flaky tail” model. Stout and colleagues demonstrated that topical introduction of recombinant FLG monomer protein covalently linked to the human immunodeficiency virus transactivator of transcription-derived cell-penetrating peptide (RMR) protein motif resulted in internalization and processing in epidermal cells. This treatment was sufficient to restore the normal phenotype in the flaky tail mouse model. Additionally, tissue penetration and cellular uptake of FLG were dependent on RMR. These findings support exploration of this strategy in the treatment of atopic dermatitis and other genetic barrier defect disorders. See page 423

In through the Skin

FLG mutations are positively associated with atopic dermatitis (AD) and transepidermal water loss. These mutations offer the opportunity for environmental allergens and food proteins to contact the immune system. Flohr and colleagues demonstrated that early-onset AD and disease severity as well as skin barrier defects were associated with food sensitization in a study of 619 breastfed 3-month-old infants. FLG mutation, however, was not an independent risk factor for food sensitization. The relationship between food sensitization and atopic disease suggests a possible role of cutaneous antigen-presenting cells in allergies. See page 345

Cell Reprogramming

In light of recent efforts to alter cellular fate through the introduction of specific factors, Chen and colleagues reported that the introduction of two transcription factors (KLF4 and p63) was sufficient to convert human fibroblasts to keratinocyte (KC)-like cells, which exhibited global gene expression, morphology, and chromatin status similar to those of KCs. Additionally, these factors induced a KC phenotype in a cancer cell line. These studies serve as an important starting point to determine which factors will further differentiate these induced KCs to functional KCs capable of epidermal tissue formation for use in regenerative therapies for the many epidermal diseases. See page 335

On the TRAIL

Metastatic melanoma carries a high mortality due to resistance to chemotherapy and the antitumor immune response, stemming from defects in proapoptotic signaling. Berger and colleagues demonstrated that the pan-RAF inhibitor L-779,450 inhibited cell proliferation in melanoma. Furthermore, this inhibitor enhanced apoptosis with the death ligand tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) and overcame resistance to TRAIL-induced apoptosis in melanoma cells. These findings suggest that enhancement of TRAIL sensitivity may support an antitumor immune response. Thus, TRAIL receptor agonists together with RAF inhibitors should be examined more extensively for their potential for melanoma therapy. See page 430

Variability of Variants

Liang and colleagues examined single-nucleotide polymorphisms in 38 melanoma candidate genes in 504 individuals from melanoma-prone families with and without accompanying mutations in CDKN2A, which may confer risk for the development of dysplastic nevi (DN). DN is a strong risk factor for melanoma. In this study, CDK6 and XRCC1 variants were significantly associated with DN susceptibility. Interestingly, neither of these genes was associated with cutaneous metastatic melanoma, and the association with CDK6 was restricted to patients with CDKN2A mutations, suggesting that variants may contribute to DN risk independently of their relationship with melanoma. See page 481