The Cannabinoid Receptor Type 2 Agonist Lenabasum Improves Symptoms of Dermatomyositis

In a phase 2 single-center, double-blind, randomized, placebo-controlled trial, Werth et al. evaluated the safety and efficacy of lenabasum treatment in 22 adult patients with refractory cutaneous dermatomyositis. Lenabasum is an agonist of cannabinoid receptor type 2, which is expressed on activated immune cells and promotes the return of the immune response to normal levels by modulating the expression of inflammatory molecules and macrophages. Cutaneous Dermatomyositis Disease Area and Severity Index scores improved in patients treated with lenabasum compared with that the scores in those treated with placebo. In addition to reductions in IFN-β and IFN-γ levels, a significant reduction in IL-31 was observed in patients who responded to lenabasum treatment concomitant with improvement in objective itch measures. Lenabasum treatment was safe and well-tolerated by the trial participants, supporting additional larger trials. See page 2651.

Variants in LSS Gene Underlie Palmoplantar Keratoderma-Congenital Alopecia Syndrome Type 2

Yang et al. employed whole-genome sequencing to uncover biallelic variants in the LSS gene, which functions in cholesterol synthesis and alternative oysterol synthesis, in two unrelated sporadic cases of palmoplantar keratoderma-congenital alopecia syndrome type 2 (PPKCA2) in patients of Chinese Han ethnicity. Further examination of these variant proteins showed alternative splicing, an N-terminal truncation in LSS protein, and overall reduced expression. These pathogenic variants altered LSS protein structure and led to decreased enzymatic activity. Consistent with the severe skin hyperkeratosis of the palms and soles in these two patients, abnormal cornified envelope formation was noted. These findings underscore the role of lipid and cholesterol homeostasis in epidermal keratinization and hair development and suggest that modulation of lipid abnormalities may serve as therapy for PPKCA2. See page 2687.

Microbiome Changes Associated with Cutaneous Squamous Cell Carcinoma

Although the gut microbiome has been linked to several cancers, characterization of the skin microbiome with respect to cancer is scarce. Voigt et al. utilized whole-genome shotgun sequencing to characterize the skin microbiome in squamous cell carcinoma (SCC) and its precursor actinic keratoses (AKs) in comparison with healthy skin, revealing a loss of diversity in the tumor microenvironment due to decreased number of species and a gradual shift from healthy skin to AK and then SCC. The commensal species *Cutibacterium acnes* was decreased with a concomitant increase in the pathobiont *Staphylococcus aureus* in AK and SCC compared with that in healthy skin. Further refinement of these differences in composition or functional gene changes may illuminate biomarkers for progression, severity, or even treatment response. See page 2773.

Dupilumab Skews the Immune Response Toward T Helper Cell 17–Related Disorders

The IL-4/IL-13 antagonist dupilumab, which has been approved to treat atopic dermatitis, asthma, and nasal polyposis, has been occasionally associated with T helper (Th) cell 17 inflammation. From an analysis of more than 37,000 dupilumab adverse drug reactions reported in the World Health Organization pharmacovigilance database, Bridgewood et al. found that dupilumab was linked to some Th17-skewed spondyloarthropathy diseases (seronegative arthritis, psoriasis, enthesitis/enthesopathy, and iridocyclitis) but not to others (ankylosing spondylitis and inflammatory bowel disease). In addition, dupilumab was not correlated with the polygenic humoral–mediated autoimmune diseases rheumatoid arthritis and systemic lupus erythematosus. See page 2660.

**TERT**<sup>−124[C>T]</sup> Promoter Mutation Is a Biomarker of Aggressive Primary Melanomas

**TERT** promoter mutations are extremely common in melanoma and are often associated with increased tumor thickness and poor survival; however, the use of these mutations as biomarkers for prognosis has proved challenging. Chang et al. reported that **TERT**<sup>−124[C>T]</sup> is associated with a more aggressive melanoma phenotype and is an independent predictor of shorter recurrence-free and overall survival. The presence of the germline polymorphism rs2853669 in combination with this variant led to significantly shorter recurrence-free and overall survival, and this relationship was stronger in superficial spreading melanoma than in nodular melanoma. See page 2733.