Keratinocyte Origin of Polyomavirus-Negative Merkel Cell Carcinoma

The cells of origin and transformation process of Merkel cell carcinoma (MCC) remain opaque. Although the majority of MCCs are associated with Merkel cell polyomavirus, virus-negative MCCs are often observed adjacent to UV-related epithelial tumors, including squamous cell carcinomas (SCCs). Kervarrec et al. reported shared somatic mutations, similar copy number variation profiles, and comparable mutational signatures between paired MCC and SCC lesions, suggesting a keratinocyte origin of the MCC part of the virus-negative MCC. Further comparison of these two tumor types revealed that inactivation of RB1 occurs as an essential step for neuroendocrine differentiation of the tumor cells and that decreased histone methylation may promote transition and growth of the tumor cells. See pages 507 and 516.

Comparison of Bulk Versus Single-Cell Gene Signatures

RNA sequencing has uncovered detailed pathologies for dermatological diseases. Bulk-tissue RNA sequencing and single-cell RNA sequencing have been leveraged in dermatology research, and each has benefits and challenges. Chung et al. compared the two different approaches through analysis of published datasets from skin samples from patients with atopic dermatitis. Both methods identified upregulated immune-response genes, whereas single-cell RNA sequencing was most useful in identifying cellular subsets or masked genes from each individual cell type. In contrast, bulk RNA sequencing identified upregulated genes from cell types likely to be filtered out in single-cell methods. These findings indicate the importance of the selection of appropriate tools for particular studies. See page 717.

Localized Small Fiber Neuropathy Underlies Lichen Simplex Chronicus

Lichen simplex chronicus (LSC) is characterized by pruritus of unknown cause. Other conditions characterized by chronic itch have been associated with changes in intraepidermal nerve fiber density. Sandoval et al. examined 33 patients with primary LSC who experienced itch and pain. These patients showed reduced sensitivity to warm and cool stimuli with concomitant normal mechanical sensitivity response. In addition, allodynia and reduced intraepidermal nerve fiber density were observed at the lesion sites, suggesting localized small fiber neuropathy underlies itch in LSC. Treatment of lesions with a 5% lidocaine plaster for 12 hours per day for 1 month significantly reduced itch, increased epidermal reinnervation, and improved thermal sensory function, supporting further investigation into therapeutic blockade of the damaged intraepidermal fibers as a treatment modality in LSC. See page 731.

Reactivation of Latent Herpesviruses in Chronic Skin Disorders Treated with Immune Suppression or Modulation

Immunosuppressive treatments, which are the mainstays of treatment for many chronic skin diseases, may induce reactivation of herpesviruses, such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV), which affect the majority of individuals globally. Speth et al. found that patients with immunotherapy-refractory chronic skin diseases showed higher rates of latent infection and subclinical reactivation of EBV and CMV infections than immunocompromised patients with chronic skin diseases. Treatment of patients with immunotherapy-refractory chronic skin diseases with antivirals led to improvement of skin lesions. This study supports greater vigilance for herpesvirus reactivation in immunosuppressed individuals with chronic skin diseases to inform clinical decision-making. See page 549.

Chronic DNA Damage Linked to Photosensitivity in Lupus Patients

Berndt et al. reported that patients with lupus with heterogeneous mutations in TREX1 showed photosensitivity. UV exposure induced increased formation of ROS that triggered DNA damage, including the increased formation of DNA double-strand breaks and cyclobutane pyrimidine dimers. This UV-induced DNA damage induced an IFN-1 response that was dependent on cyclic GMP-AMP synthase. Senescence was significantly higher in UV-irradiated TREX1-deficient cells than in normal cells. Together, these findings indicate that UV-induced inflammation in photosensitive patients with lupus stems from activation of DNA damage and repair pathways, suggesting that patients with TREX1 deficiency may benefit from efforts for UV protection. See page 633.