Loss of Cilia Evokes Pathway Switching in Resistant BCC
Basal cell carcinomas (BCC) depend on deregulated Hedgehog (HH) signaling, which relies on the primary cilium. HH inhibitors, such as Smoothened inhibitors, prevent BCC growth, but development of resistance is common. Kuonen and colleagues showed a correlation between BCC resistance and loss of primary cilia. This study also revealed an inverse relationship between the primary cilium and Ras/MAPK pathway activation, implicating a switch from HH to Ras/MAPK pathway as a mechanism of BCC resistance to HH inhibitors. Loss of cilia reduced HH signaling in these lesions, rendering them permissive for dominant oncogenic Ras/MAPK pathway activation. These findings suggest the adjunct use of MAPK inhibitors or targeting of the crosstalk between cilia and Ras/MAPK for treating BCC. See page 1439.

Shared and Discordant Signatures of AD and Psoriasis
Although it has been suggested that psoriasis and atopic dermatitis (AD) are on the same disease “spectrum,” Tsoi and colleagues identified distinct gene sets that distinguish the two diseases, including IL-17 in psoriasis and IL-13/IL-4 in AD. These investigators performed a large-scale transcriptomic study including 147 samples from patients with psoriasis, AD, and matched healthy controls to compare molecular pathophysiology. These studies identified a core transcriptome that is shared between these diseases and highlighted distinct differences in cytokine signatures between the two. Additionally, uninvolved skin from patients with psoriasis and AD exhibited a pre-inflammatory signature for both diseases. The identified gene signatures may inform drug-target prediction for therapeutic design. See page 1480.

Molecular Complexity and Evolution of Acral Melanoma
In an effort to reveal genomic variation of acral melanomas at different hierarchical levels, Zhang and colleagues combined laser capture microdissection and whole-genome amplification with multiple annealing and looping-based amplification cycles, maximizing the heterogeneity of the information gleaned from very small tumor samples from seven patients. Genomic heterogeneity, based on copy number and single nucleotide variation, was observed between tumor and nevi, among patients, among different cellular phenotypes within the same tumor, and among adjacent tumor cell clusters with an identical appearance. Beyond providing insight into the pathogenesis of acral melanoma, an aggressive subtype with poor prognosis, elucidating the genomic heterogeneity of acral melanoma also provides an important step toward a more personalized therapy. See page 1526.

Natural Solar Radiation Exposure Dampens T-Cell Response
The Australian Ultraviolet Radiation and Immunity Study sought to determine the effects of sun exposure on the primary immune response to a T cell—dependent protein antigen in an effort to thoroughly delineate the immunomodulatory properties of UVR exposure in a natural setting. In 217 healthy adults, higher natural solar UVR exposure at antigen sensitization phase reduced the antigen-specific T cell—mediated immune response to keyhole limpet hemocyanin but evoked no detectable alterations in the antibody response. A reduced delayed hypersensitivity response and decreased proportion of T helper type 17 cells were also measured. Interestingly, no association was observed between immunization response and lifetime UVR exposure or vitamin D levels. See page 1545.

Inflammatory Cytokines in Psoriasis Promote Immature Keratinocyte State
Using markers of differentiation and stemness, Ekman and colleagues characterized a more immature phenotype of keratinocytes from the germinative compartment in psoriasis lesions. In the presence of tumor necrosis factor-α, IL-17, and IL-22, the key inflammatory cytokines implicated in psoriasis pathogenesis, keratinocytes showed an increased stem cell marker expression and stemness phenotypes, including enhanced proliferation, proliferation-like morphology, and colony-forming capacity. Inhibitors to RAC1, MAPK/ERK kinase, extracellular signal—regulated kinase, and NF-κB abolished these cytokine-induced changes, indicating that IL-17 and IL-22, in the psoriasis microenvironment, act directly on keratinocytes to promote proliferation and stemness via this molecular pathway. See page 1564.