Trade-off between skin protection programs

Following sun exposure, the skin activates two protection programs. Within minutes, the UV radiation stress response involving proliferation, inflammation, DNA repair and the immune system is activated, and then within hours and days of exposure, pigment production by epidermal melanocytes occurs. Both responses provide sun protection, but the mechanisms regulating these temporally differing responses remain unclear. Malcov-Brog and colleagues demonstrated that UVB exposure every 48 h induces greater skin pigmentation than exposure every 24 h without an associated increase in the stress response. These investigations revealed that the transcription factor MITF serves as the UV-protection timer. This factor, which is the central regulator of the melanocyte lineage, first activates cell survival and then pigmentation in response to combinatorial effects of multiple negative regulatory loops involving HIF1α at the transcriptional level and microRNA-140a at the post-transcriptional level. These mechanistic insights suggest that MITF serves to control the trade-off between the two skin protection programs in an effort to curb skin damage by UV radiation. (Molec Cell 72:444-456, 2018) Selected by C. Niessen

Posttranscriptional mechanisms to enhance IL-17-driven inflammation

The inflammatory cytokine interleukin (IL)-17 functions in host defense against microbial pathogens and drives immunopathology in autoimmunity. Therapeutic targeting of this cytokine has been efficacious for psoriasis, highlighting the need to fully understand the mechanisms relevant to IL-17 function. One such mechanism involves promotion of mRNA stability. Amatya and colleagues found that IL-17 increased the levels of the RNA-binding protein AT-rich interactive domain-containing protein 5A (Arid5a) in mouse mesenchymal cells and in human keratinocytes. Arid5a promoted IL-17-driven immunity by binding to the 3’UTR regions of target mRNAs to stabilize IL-17-induced transcripts encoding immune effectors (IL-6 and CXC chemokines). Arid5a also interacted with the translation initiation complex to facilitate IL-17-induced translation of the transcription factors C/EBPβ and IkBζ, which are implicated in autoimmunity and chronic inflammation. These factors then activated IL-17-dependent targets, further promoting IL-17-driven inflammation and immune responses. Thus, Arid5a integrates multiple IL-17 signaling pathways to promote post-transcriptional control of mRNAs involved in immunity and inflammation, providing insights into targeting strategies for autoimmunity and chronic inflammatory diseases. (Sci Signal. 11:eaat4617, 2018) Selected by M. Udey

Non-genetic mechanism for BCC relapse

Although most patients treated with the hedgehog (Hh) inhibitor vismodegib experience clinical benefit, BCC tumors commonly respond but recur after treatment discontinuation without development of genetic mutations that are known to cause treatment resistance. Sánchez-Danés and colleagues reported that vismodegib promotes tumor cell differentiation, thereby inducing BCC regression. In two mouse models and in patients, these investigators identified a tumor cell population that expresses the Wnt signaling molecule LGR5, is characterized by active Wnt signaling, persists after treatment, and promotes tumor regrowth after drug discontinuation. Interestingly, the vismodegib-induced tumor state is not only reversible upon drug discontinuation but also re-inducible upon reintroduction of drug. Additionally, dual Wnt and Hh inhibition eliminated the persistent LGR5+ tumor cells induced by vismodegib administration, leading to tumor eradication. These findings provide insight into the molecular underpinnings of BCC relapse and suggest that dual Wnt and Hh inhibition may be a clinically relevant strategy to prevent relapse of BCC and other tumors that rely on Hh and Wnt activation. (Nature 562:434-438, 2018) Selected by I. Brownell

RNA sequencing data reveals insights into psoriasis

Merleev and colleagues utilized four RNA-sequencing datasets to mine the human skin transcriptome to investigate patterns of T cell receptor (TCR) usage and differences in zβ and γδ T cell responses in psoriasis. These studies uncovered a statistically significant association between TRAJ23 and psoriasis and the psoriasis-associated cytokine IL-17A. In addition, the TCR-γ segment TRGV5 was also associated with psoriasis; however, this segment was associated with IL-36A and IL-17C and not IL-17A. Moreover, the expression of TCR- γδ was mildly elevated, but relatively low overall, in psoriatic skin compared to TCR- zβ genes, in contrast to prior assertions that γδ T cells were preferentially expanded over zβ T cells in psoriasis. This approach not only sheds light into TCR usage in psoriasis but also supplements other methods, such as single-cell analysis, that have been used to study psoriasis pathobiology. This approach may be useful in studies of other immune-mediated diseases, immune responses, or tumor-infiltrating immune responses. (JCI Insight. 10.1172/jci.insight.120682, 2018) Selected by J. Celfand

Skin regeneration promoted by aging

Scar formation or tissue regeneration are possible wound repair responses Mammals most often repair injured tissue with scar formation, although a few human tissue regeneration examples are known. Wounds in older individuals typically heal with thinner scars than those in younger individuals, suggesting that tissue regenerative pathways may actually become more effective with aging. Nishiguchi and colleagues found that secreted stromal-derived factor 1 (SDF1) promoted scar formation in young mice and that deletion of this factor in the young mice improved tissue regeneration. Moreover, aging suppressed SDF1 activation by remodeling chromatin accessibility to the SDF1 gene via increased recruitment of enhancer of zeste homolog 2 (EZH2) and histone H3 lysine 27 trimethylase to the SDF1 gene promoter. Further studies in human cells and organoids revealed that human skin also exhibits age-dependent SDF1 suppression, suggesting that inhibition of SDF1 or EZH2 may have clinical relevance for decreasing scar formation and highlighting a unique example of enhanced tissue function in aged animals. (Cell Rep. 24:3383-3392, 2018) Selected by M. Detmar