**Vitiligo responds to IL-15 blockade**

Vitiligo results from CD8+ T cell targeting of melanocytes, leading to patchy depigmentation. Upon cessation of therapy, depigmentation recurs at the same locations, implicating resident autoimmune memory T (TRM) cells. Indeed, Richmond and colleagues found that vitiligo patients have antigen-specific autoreactive TRM cells in lesional skin. As interleukin (IL)-15 is critical for generation of TRM cells, these investigators examined the effects of blocking IL-15 signaling via an antibody to the IL-15 CD122 subunit, which is expressed on autoreactive TRM cells in vitiligo. In a mouse model of vitiligo, treatment with this antibody reversed established disease. Importantly, short-term treatment for only 2 weeks resulted in significant repigmentation that lasted for 10 weeks, supporting future clinical trials testing the durability of this response in human vitiligo patients. *(Sci Transl Med. 10.1126/scitranslmed.aam7710, 2018)*  

**Molecular signature of rapid wound healing in the oral mucosa**

Wounds in the oral mucosa heal much more rapidly and with far fewer complications than those in the skin. To compare the molecular mechanisms underlying these differences, Iglesias-Bartolome and colleagues compared the transcriptional profiles of wounds in the oral buccal mucosa and those in the skin over time. The oral mucosa appears to be primed for rapid wound healing with limited differentiation of oral keratinocytes and proinflammatory responses. Transcriptional regulators PAX9, PITX1, PITX2, and SOX2 as well as other genes comprise the specific wound-activated transcriptional network that is present in oral mucosa. Specifically, SOX2 and PITX1 regulate networks involved in wound healing and were able to reprogram skin keratinocytes to exhibit accelerated wound resolution. Together, these findings shed light on the differences between wound healing in the oral mucosa and the skin and highlight molecules that may be useful targets to improve wound healing and reduce scarring. *(Sci Transl Med. 10.1126/scitranslmed.aap8798, 2018)*  

**Prenatal delivery of Fc-EDA restores sweat glands**

Loss-of-function variants of the ectodysplasin A (EDA) gene are known to underlie X-linked hypohidrotic ectodermal dysplasia (XLHED), a potentially life-threatening disorder in which sweat gland development is irreversibly compromised. Previous studies demonstrated that administration of recombinant EDA fused with the constant domain of IgG1 (Fc) into the circulation or amniotic fluid in mice resulted in correction of the disease phenotype. Schneider and colleagues recently treated two women pregnant with fetuses (twins and singleton) that were diagnosed with XLHED with intraamniotic injection of Fc-EDA at 26 weeks gestation. All three infants exhibited the presence of sweat glands and normal sweating, as well as development of teeth and salivary and meibomian glands, during the first years of life via uptake of recombinant Fc-EDA from amniotic fluid. These results were dependent on the presence of the Fc receptor, which facilitates uptake of recombinant EDA presumably through the gut, offering a potential new mechanism for protein-replacement therapy for XLHED. *(N Engl J Med. 378:1604-1611, 2018)*  

**Targeting neuron hyperexcitability to reverse PDN**

Painful diabetic neuropathy (PDN) stems from sensory neuron hyperexcitability that involves spontaneous dorsal root ganglion (DRG) nociceptor axon and C-fiber nociceptor terminal activity, resulting in neuropathic pain and small-fiber degeneration. As safer and more effective therapies are needed to treat intractable PDN, Jayaraj and colleagues sought to identify molecular pathways that link hyperexcitability to PDN pain and small-fiber degeneration. Their studies identified chemokine CXCL12/CXCR4 signaling in the initiation of mechanical allodynia and small-fiber degeneration in PDN. Activation of CXCR4 receptors increased the excitability of DRG neurons that express the NaV1.8 sodium channel, and allodynia and small-fiber degeneration could be prevented by deletion of the CXCR4 receptor or by chemogenetic inhibition of the excitability of these DRG neurons. Thus, implication of CXCR4 signaling in hyperexcitability of NaV1.8-positive DRG neurons offers potential targets for development of therapies for PDN patients to improve quality of life. *(J Clin Invest. 128:2205-2225, 2018)*  

**Virotherapy enhances anti-PD1 response in melanoma**

Antibodies to programmed death protein 1 (PD-1) or its ligand are used to induce long-lasting antitumor responses in cancer patients; however, the response rate is limited especially in a subset of patients who lack intralesional CD8+ T cells. Based on prior success of other studies of combination immunotherapy to alter the immune-suppressive tumor microenvironment and enhance response to another biologic ipilimumab, Ribas and colleagues conducted a phase I/II trial of intratumoral injection of the genetically modified herpes simplex virus talimogene laherparepvec in combination with treatment with the anti-PD1 agent pembrolizumab in 21 advanced melanoma patients. The objective response was 61.9%, with a complete response rate of 33.3%, and these responses were independent of baseline CD8+ infiltration or interferon-γ signature. Furthermore, these responses were characterized by a systemic increase in circulating CD4+ and CD8+ T cells, increased tumor CD8+ T-cell infiltration, and expression of PD-1 on T cells and PD-L1 on tumor cells. This increased response was greater than that expected with either therapy alone and featured a low rate of toxicities, which were common to single-agent use. These promising results have spurred a follow-up phase 3 trial to further test the combination of systemic pembrolizumab combined with intralesional injection of talimogene laherparepvec in more than 600 patients. *(Cell 170:1109-1119, 2017)*  

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