Long-Term Success for Junctional Epidermolysis Bullosa Gene and Cell Therapy

Generalized junctional epidermolysis bullosa features recurrent blistering and chronic wounds that are susceptible to infection, leading to decreased QOL and a 40% mortality rate before adolescence. In a previous study, genetically corrected autologous epidermal cultures were transplanted to a boy aged 7 years with inherited junctional epidermolysis bullosa caused by a homozygous mutation in LAMB3, which encodes the hemidesmosome component laminin 332-β3. Early reports indicated an almost complete, fully functional epidermis after the transplantation. Kueckelhaus et al. recently reported the long-term clinical and functional outcomes for this patient 65 months after transplantation. Detection of a physiologic number of Langerhans’ cells, intact skin barrier, and the presence of sebaceous and sweat glands supported the notion that transgenic epidermal cultures can restore a functional epidermis replete with immune cells and maintenance of epidermal hydration. The skin exhibited mild fibrosis, erythema, and mild neuropathy without any evidence of γ-retroviral vector-related adverse events. This long-term follow-up suggests that early transplantation may improve clinical and functional outcomes in patients with junctional epidermolysis bullosa. (N Engl J Med 385:2264–70, 2021; https://doi.org/10.1056/NEJMoa2108544) Selected by L. Brucker-Tuderman

GPR15L Functions in the Immunological and Structural Barrier of the Epidermis

The GPR15L is an antimicrobial protein that is ubiquitously expressed in epithelial tissues, and its receptor GPR15 has been implicated in chemotactic activity for epidermal T cells. However, the role of GPR15L in keratinocyte differentiation and barrier formation remains obscure. Dainichi et al. showed that GPR15L was highly induced during skin inflammation and that this factor stimulated the expression of inflammatory factors and reduced the expression of barrier components in keratinocytes. Mice deficient in GPR15L exhibited a mitigated response of keratinocyte to lipopolysaccharide and reduced skin inflammation after imiquimod treatment. Induction of GPR15L was involved in the impairment of the skin barrier during inflammation but was not essential for the steady state. Taken together, these findings suggest a keratinocyte-intrinsic role for GPR15L in skin inflammation and barrier regulation and highlight the potential for its function beyond its antimicrobial properties. (Front Immunol 13:825032, 2022; https://doi.org/10.3389/fimmu.2022.825032) Selected by M. Wittmann

Papillary Fibroblasts Repair UVR-Induced Damage

Extensive studies have characterized the consequences of UVR to the epidermis, extracellular matrix (ECM), and immune cells in the skin; however, few have examined the short- and long-term effects of UVR on dermal fibroblast subpopulations. Rogoni et al. found that acute UVR exposure results in transient loss but subsequent replenishment of papillary fibroblasts, whereas chronic UVR induces long-term loss of papillary fibroblasts without replenishment and substantial ECM reorganization. The fibroblast depletion was primarily the result of apoptosis and was not associated with cell migration at early time points, although after 4 days, the fibroblasts were more motile, concomitant with ECM remodeling and fibroblast redistribution. Dermal fibroblast survival was enhanced by cutaneous T cells that infiltrated the dermis and became activated during UVR as well as by prostaglandin E2/EP4 receptor signaling. Furthermore, inhibition of cyclooxygenase 2, an enzyme critical for proinflammatory prostaglandin synthesis, reduced loss of dermal fibroblasts after UVR exposure, suggesting that this factor may be targeted for therapeutic applications in the prevention of UVR-induced photoaging and skin damage. (eLife 10:e71052, 2021; https://doi.org/10.7554/eLife.71052) Selected by M.C. Udey

Insular Cortex Forms Immune-Related Representations

In an effort to determine how the brain evaluates and represents the state of the immune system, Koren et al. investigated the posterior insular cortex (InsCtx), which is the primary cortical site of integration, integrates multiple information sources, and is situated to gather immune-related information through peripheral neurons that respond to immune signals. Using two mouse models, dextran sulfate sodium–induced colitis and zymosan-induced peritonitis, these investigators found increased neuronal activation in the InsCtx after induction of these disease states. The neuronal activity and immune response were unique in each situation. Mere reactivation of InsCtx neurons captured during colitis or peritonitis led to the recapitulation of the inflammatory state confined to the colon or peritoneum, respectively. These observations indicated that the brain can reactivate previously acquired information regarding the immune response and induce inflammation through a direct connection by peripheral neurons with the sites of inflammation. Inhibition of the InsCtx dampened the clinical symptoms and immune responses in the colitis model, suggesting that targeting this brain region may serve as a therapeutic strategy for colonic inflammation control. (Cell 184:5902–15, 2021; https://doi.org/10.1016/j.cell.2021.10.013) Selected by I. Brownell

Structural Studies of Mas-Related G Protein-Coupled Receptors

The Mas-related G protein-coupled receptors (MRGPRs) MRGPRX2 and MRGPRX4 have been implicated as targets that mediate mast cell degranulation/itch-related hypersensitivity reactions and cholestatic itch, respectively. Cao et al. described single-particle cryoelectron microscopy structures of MRGPRX2 in complex with a small molecule agonist (R)-ZINC-3573 and the peptide cortistatin-14 as well as those of MRGPRX4 with a specific agonist. These structures revealed that these agonists bind near the extracellular solvent, which differs from the orthosteric binding sites of other G protein-coupled receptors. These observations support a unique ligand transduction mechanism in this family of receptors. The agonists and antagonists analyzed in these studies offer chemical probes for additional investigation of the molecular structural and functional properties of these MRGPRs, and the information gleaned from these structures will guide the discovery of therapeutic molecules for pain, itch, and mast-cell hypersensitivity. (Nature 600:170–5, 2021; https://doi.org/10.1038/s41586-021-04126-6) Selected by E. Lerner