Skin: Uncovering Our Covering

Michele de Luca (University of Modena, Italy) concluded his talk then paused and looked out across the auditorium. The response of those attending the 2017 Congress of the European Society of Gene & Cell Therapy (Berlin, Germany) was immediate and rapturous. De Luca had just presented a case study in which a seven-year-old boy suffering from a devastating skin disease had been saved by regenerating the majority of his epidermis. As detailed in the recent publication in Nature, this success story represented the culmination of years of intense research into epidermal biology, highly-skilled surgeons conducting painstaking skin grafts, and a tirelessly dedicated team of healthcare professionals assisting with pain management and rehabilitation. This tour de force spared the boy from almost certain death and highlighted the huge potential that similar gene-and-cell therapeutic approaches could have on debilitating genetic diseases.

The disease in question was junctional epidermolysis bullosa (JEB), a severe and often fatal genetic disease in which mutations in basement membrane proteins (in this case laminin b3) prevent the epidermis from attaching to the underlying dermis. The child had suffered from JEB from birth, but infections had exacerbated the condition and at the time of the first skin graft ~80% of his epidermis was absent. In an attempt to overcome these life-threatening wounds, a skin biopsy was taken from a non-blistered region and primary keratinocyte cultures were grown, transduced with a retroviral vector containing a full-length version of laminin b3 coding sequence, and expanded. A total of 0.85 m² transgenic epidermis was grafted onto the affected regions of the boy, in three separate procedures. The approach worked. Two years on, the autologous grafts remain fully functional and the boy is now able to live a normal active life. Aside from its astonishing clinical success, this study also resolved a long-standing question in skin biology as to whether skin renewal occurs via differentiation of a large population of progenitor cells, or a smaller number of long-lived founder stem cells. Clonal tracing analysis indicated that the transduced epidermis consisted of a restricted number of cell populations, thus favoring the latter scenario.

It is perhaps surprising, given that the skin is the largest and most accessible organ in humans, that such fundamental processes are still being defined. However, the skin comprises a complex mix of cell types and tissues that are exquisitely engineered to perform a vast array of functions. The epidermis is the outermost layer that acts as a physical barrier to harmful pathogens and chemicals. It largely comprises keratinocytes, but there are also pigment-producing melanocytes and Langerhans cells that alert the immune system to the presence of pathogens. The skin also supports diverse populations of epidermal microbiota whose functions in human health and diseases are still being delineated. Connecting the epidermis is the dermis, a layer that provides strength and elasticity due to the presence of collagen and elastin. It also harbors blood and lymphatic vessels, sweat, sebaceous and apocrine glands, hair follicles and nerve endings. The hypodermis underlies the dermis and contains adipocytes that form an insulating and protective layer of subcutaneous adipose tissue (SAT). Taken together, the skin performs many crucial protective, structural, immunological, metabolic, endocrine, exocrine, regenerative, sensitive, adaptive, and microbiological functions.

But the list does not stop there, and studies continue to uncover additional cutaneous surprises. A fascinating example, published in Science Translational Medicine on November 8, 2017, revealed that wound healing has a circadian component. The study found that fibroblasts migrate towards wounds and proliferate more efficiently during a mouse's active phase. This wound-healing response is governed by circadian actin dynamics that drive processes such as cell migration and adhesion. To test if this observation had clinical significance, post hoc analysis of human burns victims found that burns inflicted during the daytime healed ~60% faster than nighttime burns. Of course, this type of analysis does not offer mechanistic proof that circadian actin dynamics are responsible, but it does support the rodent data and provides fascinating evidence that the performance of human skin is diurnally influenced. A clinical application might be to apply chronoactive agents to wounded skin, or prior to surgical procedures, to promote maximal healing.

What is increasingly appreciated is the impact chronic skin disorders may have on the entire body. Psoriasis, for example, which was traditionally viewed as a disorder of the skin, is now regarded as a systemic inflammatory disorder associated with wider comorbidities. As detailed on the National Psoriasis Foundation's website, these include an increased risk of developing obesity-related complications such as Type 2 Diabetes and dyslipidemia, and vascular complications including hypertension, myocardial infarction and stroke. What are the mechanisms that link chronic skin disorders to wider systemic events? Ongoing research suggests that the endocrine function of the skin may play a role. Keratinocytes and skin-resident immune cells have been shown to secrete a variety of pro-inflammatory molecules, many of which are up-regulated in psoriatic patients. One theory is that these pro-inflammatory molecules can act on nearby SAT, causing a disruption in its own adipocytokine secretion, immune cell infiltration and escalation of an inflammatory phenotype. This biochemical perfect storm decreases insulin sensitivity and the SAT’s capacity to store lipid, resulting in the deposition of fat in visceral organs and progression towards diabesity.

One intriguing possibility is that effective treatment of a chronic skin condition might also decrease the risk and/or severity of cardiometabolic disorders. According to The Lancet's Global Burden of Disease 2015 study, 79.7 million people globally suffer from psoriasis, highlighting the potential healthcare benefit if this hypothesis proves correct. Funding bodies should support collaborations between patients, researchers and clinicians to enable this mechanistic relationship to be fully explored. The skin is a fascinating organ whose impact on the body is anything but skin-deep.