

KGF, a multipurpose skin protector

Keratinocyte growth factor (KGF), a member of the fibroblast growth factor family, exerts both a mitogenic and a cytoprotective effect on epithelial cells in the gastrointestinal tract, lung, bladder, and hair follicles. As this factor has been used to treat patients who develop oral mucositis in response to radiation and chemotherapy, an understanding of the details of the cytoprotective effect in each tissue type is advantageous for clinical use. Braun and colleagues demonstrated that KGF protected hair follicle epithelial cells from apoptosis in the presence of cytotoxic stress by reactive oxygen species and electrophilic agents. Interestingly, this growth factor also protected the epithelial cells from UV damage. KGF conferred protection through binding of the high-affinity receptor FGFR2IIIb, activation of multiple signaling pathways, and *de novo* protein synthesis. Since this powerful effect was noted in response to chemotherapeutic agents and KGF does not promote tumor growth, future studies are warranted to investigate the potential for KGF treatment of hair follicles in patients undergoing chemotherapy for malignancies. (*J Cell Sci* 119:4841–9, 2006)

Ubiquitin protease prevents tumors

Cylindromatosis (CYLD) is a ubiquitin-carboxyterminal hydrolase, which is mutated in patients with familial cylindromatosis, characterized by tumors of the hair follicles and the sweat glands of the head and neck. *In vitro* studies suggested that this deubiquitinating enzyme downregulates NF- κ B activity; however, the role of this protein *in vivo* remains obscure. Using CYLD-deficient mice, Zhang and colleagues recently showed that this protein provides post-translational regulation for both the c-Jun N-terminal kinase and NF- κ B signaling pathways. Activation of these pathways was enhanced only in CYLD-deficient immune cells after antigen receptor stimulation. In a mouse model of colitis-associated cancer, CYLD-deficient mice exhibited an increase in intestinal inflammation and a concomitant increase in colonic tumors. This finding implicates CYLD as a tumor suppressor via its regulatory action on critical signaling pathways. (*J Clin Invest* 116:3042–9, 2006)

Epidermal barrier depends on Arnt

The aryl hydrocarbon receptor nuclear translocator (Arnt) is a transcription factor that dimerizes with multiple partners to perform functions in multiple biological pathways. Roles in the toxic response to dioxin-like pollutants and in hypoxia implicate Arnt as an important regulator of environmental adaptation; however, the molecular mechanism of these actions is not clearly defined. The epidermal barrier provides a biosensor to transduce changes in the environment. Geng and colleagues demonstrated an epidermal barrier defect in conditional Arnt

knockout mice. In addition, genetic profiling in the knockout epidermis showed upregulation of keratinocyte differentiation genes, indicating that Arnt is not merely a transcriptional activator. Understanding the effects of Arnt on the regulation of epidermal differentiation complex factors on chromosome 3, protease inhibitors, and lipid-related enzymes is critical for dissecting the coordinated expression of late epidermal differentiation genes. Taken together, these results implicate Arnt in physiological adaptation via epidermal homeostasis during the perinatal-to-postnatal transition. (*J Cell Sci* 119:4901–12, 2006)

Alternative splicing of desmoglein 1

Alternative splicing of pre-messenger RNA permits synthesis of vast numbers of proteins from a limited number of genes. This mechanism may contribute to autoimmune diseases via the production of novel lymphocyte epitopes. Mouquet and colleagues described an alternative epidermal transcript of the desmoglein 1 (*DSC1*) gene, whose protein is critical for calcium-dependent cell–cell adhesion in desmosomal junctions. Dsg1 is the autoantigen of pemphigus foliaceus (PF), a blistering skin disease involving autoantibody responses. Importantly, a peptide of the alternatively transcribed gene induced T-cell proliferation in PF patients. Several of these patients carried the major histocompatibility complex (MHC) HLA class II alleles (DR β 1*0102 and *0101), which have been implicated in genetic susceptibility to PF. These MHC alleles also exhibited high affinities for the alternative Dsg1 peptide in *in vitro* binding experiments. From these data, the authors speculated that autoreactive T cells activate specific B cells and instigate the production of the autoantibodies implicated in PF. (*J Immunol* 177:6517–26, 2006)

CCN3 mitigates melanocyte development

During development, melanocytes migrate to the epidermis and attach to the basement membrane upon contact with keratinocytes. Development of melanocytes must be tightly regulated, as these cells cannot survive in the upper epidermal layers and must remain at stable levels with respect to keratinocytes. Fukunaga-Kalabis and colleagues recently discovered that the matricellular protein CCN3 (nephroblastoma overexpressed) is upregulated in melanocytes upon contact with keratinocytes in culture. CCN3 serves to decrease the growth of melanocytes in order to regulate melanocyte spatial location and number. Interestingly, discoidin domain receptor 1 (DDR1), a receptor tyrosine kinase, was upregulated in CCN3-overexpressing melanocytes. CCN3 appears to mediate this developmental effect via collagen type IV adhesion to the basement membrane through interaction with DDR1, although other downstream effectors were implicated, as a decrease in DDR1 did not abrogate the growth inhibition. Regulation of CCN3, therefore, is essential in maintaining correct melanocyte development and homeostasis. (*J Cell Biol* 175:563–9, 2006)