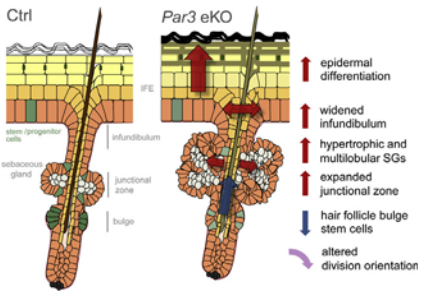
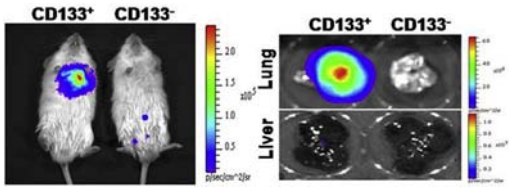
Par3 for the Course



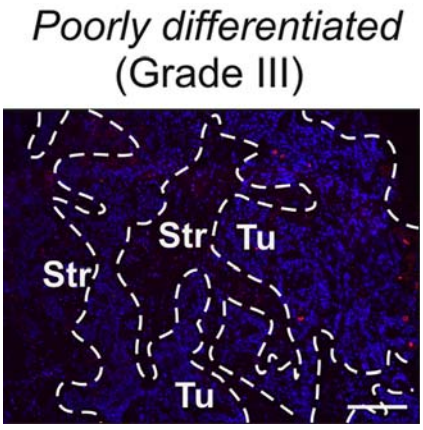
The scaffold protein partitioning-defective 3 (Par3) is known to promote tight junction formation. The embryonic lethality of germline knockout of this factor has made studying the postnatal effects of Par3 difficult. By genetically inactivating Par3 in the interfollicular epidermis and its appendages, Ali and colleagues found that Par3 loss perturbed the inside-out skin barrier, altered tight junction components, increased epithelium differentiation, induced premature activation and later decline of hair follicle stem cells, and expanded committed progenitors to increase differentiation in the sebaceous gland and interfollicular epidermis. These studies uncovered a critical role for the Par3 polarity protein in epidermal homeostasis, skin barrier integrity, and stem cell maintenance in the pilosebaceous unit. ***See page 2406***

Combatting Cancer Stem Cells



Cancer stem cells (CSCs) may be the underlying cause of aggressiveness, drug resistance, and metastasis in various cancers. Kumar and colleagues reported that melanoma-derived $CD133^+$ cells that exhibit stem cell-like characteristics function in the epidermal-mesenchymal transition and melanoma progression. Notch1 regulates CD133 expression, which activates mitogen-activated protein kinase (MAPK), ultimately leading to melanoma growth, angiogenesis, and metastasis. Importantly, inhibition of Notch1 using the novel anticancer agent andrographolide diminished expression of CD133, eliminating MAPK signaling and the tumorigenic potential of these melanoma stem cells. As cancer recurrence due to failure to respond to chemotherapy has been attributed to CSC chemoresistance, targeting Notch1 signaling may have potential therapeutic benefits for CSC-mediated melanoma progression. ***See page 2462***

MicroRNA Regulation in cSCC



MicroRNAs (miR), which regulate gene expression, have been implicated in tumor initiation and progression. Lohcharoenkal and colleagues uncovered a negative correlation between expression of the epidermal-enriched miR-203 and cutaneous squamous cell carcinoma (cSCC) differentiation grade, an important determinant of clinical tumor behavior. This miR abrogated cSCC proliferation, migration, invasion, angiogenesis, and tumor growth via targeting of the oncogene *c-MYC*, suggesting that miR-203 is a tumor suppressor in cSCC and that therefore pharmacologic restoration of miR-203 levels in cSCC may prove to be therapeutic. ***See page 2485***

Skipping Exons

Approximately 15% of patients with recessive dystrophic epidermolysis bullosa (RDEB) harbor mutations in *COL7A1* exons 73 or 80, resulting in loss of adhesion between the epidermis and dermis and severe blistering. Using specific 2′-O-methyl antisense oligonucleotides to induce exon skipping of each of these exons, Turczynski and colleagues induced deposition of functional collagen VII and anchoring fibril formation at the dermal-epidermal junction in a xenograft model. Thus, targeted *COL7A1* exon skipping may provide a feasible local or systemic treatment option for RDEB patients, similar to the success observed for this strategy in Duchenne muscular dystrophy. *See page 2387*

The Good and the Bad

The structural similarities of the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) in concert with the abilities of MR to bind both MR and GR ligands spurred the investigation of whether the adverse effects of glucocorticoids (GC), which are common as anti-inflammatory treatments for cutaneous diseases, actually stem from MR. In a MR-knockout mouse, Boix and colleagues demonstrated that MR contributed to GC-induced epidermal thinning but not reduced collagen deposition, and this receptor exerted anti-inflammatory actions similar to GR. The identified common and unique roles for MR and GR in skin indicate that these effects must be considered for prescription of GC treatment. *See page 2417*

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