suppressor CYLD. When Snail was blocked in melanoma cells, the low CYLD expression bounced back, and the cells formed smaller and less aggressive tumors when transferred into mice.

This group had previously found that Snail was abnormally abundant in melanoma cells. They now link increased Snail to a common mutation (V600E) in the kinase BRAF—found in more than half of malignant melanomas in humans—that promotes tumor growth by activating Erk signaling in response to growth factors and cytokines. Indeed, when mutated BRAF was expressed in melanoma cells, Snail levels rose and CYLD levels waned.

CYLD’s ability to suppress tumor cell division is due in part to its ability to keep the transcription factor BCL-3 out of the nucleus, where it normally teams up with NF-κB to turn on the cell cycle protein cyclin D1. This pathway was also operational in melanoma cells, the authors found. But in these cells, CYLD also inhibited the expression of N-cadherin, a protein known to promote tumor spread.

By curbing CYLD, Snail thus promotes both tumor growth and spread. Indeed, in skin cancer samples from humans, increased Snail and decreased CYLD correlated with decreased survival.

Soothing baby’s skin

It’s not ineptitude that keeps immune cells in human embryonic skin from reacting to motherly tissue. According to Schuster et al. on page 169, the cells are suppressed from the get-go.

Theories on how developing embryos prepare their immune system for adult life but keep it in check before birth have mainly been generated from studies in mice. Some hypotheses predict that embryonic immune cells are too immature or too few in number to mount an adequate response. Here, Schuster et al. study dendritic cell (DC) ontogeny in the skin of human embryos and find that the cells are functional within the first trimester but are kept in check by a suppressive environment.

DCs from embryonic skin up-regulated costimulatory molecules and stimulated T cells, proving their functional capability. But this potential may be dampened in situ by the high levels of the immunosuppressive cytokine IL-10 that the authors found in embryonic tissues.

Comparing precursors of skin-specialized Langerhans cells (LCs) from embryos of various ages revealed evidence of a stepwise progression of epidermal LC development. By the ninth week of gestation, DCs had appeared in the epidermis—likely drawn in by the high levels of chemokines expressed there and in the dermis—and appeared to be proliferating. At that time, some of the cells expressed CD1c, and only later acquired langerin and CD1a, identifying them as mature Langerhans cells.

Experimental evidence revealing the mechanisms behind DC migration, proliferation, and maturation in developing skin may be a long time coming, says Schuster, largely because of the ethical constraints involved in embryonic research.

Accounting for taste

With palates so delicate they put food critics to shame, T cell receptors distinguish tiny bumps in molecular shape, report Archbold et al. on page 209.

Although close members of the HLA-B44 family differ by a single amino acid, they aren’t interchangeable. Mismatches of HLA-B*4402 and B*4403 lead to transplant rejection. And people with B*4405 generate stronger CD8+ T cell responses against Epstein-Barr virus (EBV) than do people with either B*4402 or B*4403. Few HLA molecules have been crystallized along with their corresponding T cell receptors (TCR), so the physical basis for picky T cell preference is largely unknown.

Archbold et al. now show how just one amino acid, buried within the antigen-binding region of B*4402, B*4403, and B*4405, indirectly alters T cell recognition. Using an EBV epitope as a model, the authors found that B*4405 allowed the peptide more room to wiggle at the binding site than did B*4402 or B*4403. And that extra flexibility allowed the TCR to further change the peptide shape upon binding, allowing it to grasp onto the peptide–HLA complex more tenaciously. As a result, T cells had a 10-fold higher affinity for the peptide bound to HLAB*4405 than to the other B44 alleles.

Therefore it wasn’t the HLA polymorphism itself that altered the T cell recognition, but rather the slight shape change it caused in the bound peptide. This indirect effect probably extends to other “micropolymorphic” HLA alleles beyond the B44 family, say the authors.