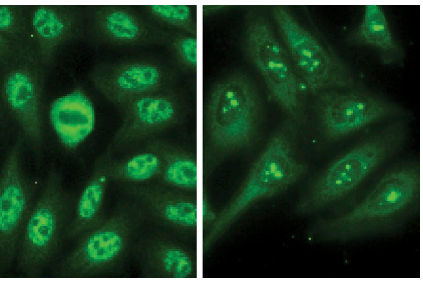


A population of mature B cells from healthy people produce autoreactive antibodies that bind to DNA (green).

Learning to tolerate ourselves

On page 139, Duty et al. find self-reactive B cells in healthy adults that might harm their own body if given the chance.

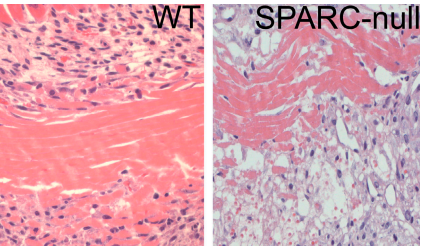
Checkpoints during B cell development ensure that immune cells won't confuse the self for an intruder. At birth, many B cells express self-reactive receptors. Most of these potentially harmful cells are either set straight by rearranging new receptors or are eliminated before leaving the bone marrow. Yet a minority manages to escape, slipping into the periphery as mature B cells with a propensity for self-attack.

In healthy mice, autoimmunity is avoided because most self-reactive escapees, which classically express high levels of IgD and reduced IgM, are arrested in an anergic state. But until now, a similar population of anergic, autoreactive B cells hadn't been found in humans.

Duty et al. have now spotted these cells in the blood of healthy adults, where they accounted for 2.5% of peripheral B cells. These cells turned out to be mature and autoreactive, bearing no signs of antigen encounter in vivo. The cells were also anergic, as they had faulty signaling in response to BCR ligation. These defects were overcome, however, when the authors gave cells a strong enough signal.

Autoreactive B cells are common in patients with autoimmune diseases, such as lupus or rheumatoid arthritis (RA). And the authors suspect that the new population may contain the precursors of these troublemaking cells. Lapses in early steps of self-tolerance have been shown to contribute to disease in patients with lupus or RA. Alternatively, suggests author Patrick Wilson, anergy may fail in these patients, allowing self-sabotaging cells to run free.

Why the body silences these potentially mutinous cells after they escape rather than putting them to death is unclear. Perhaps, suggests Wilson, a limited amount of autoimmunity isn't such a bad thing, as long as it's not chronic. For example, anergic cells might help attack pathogens disguised as self-antigens.



Collagen formation was disorganized in SPARC-less mice, leaving them vulnerable to cardiac rupture.

No spark can break a heart

A little SPARC may help a broken heart rebound, according to Schellings et al. on page 113.

Like other extracellular matrix proteins, SPARC helps to heal wounds by modulating cell–matrix interactions and promoting cell proliferation, migration, and angiogenesis. Here, Schellings et al. find that SPARC uses its wound-healing skills to form strong scars that help prevent cardiac rupture after a heart attack.

Mice lacking SPARC developed normal, healthy hearts. But after a heart attack, SPARC-less mice—particularly males—had a hard time recovering. Without the protein, which is known to bind directly to type I collagen, the normally strong and structured collagen bundles that form at the site of injury were loose, creating a disorganized scar. Similar collagen defects are seen in healing skin when SPARC is absent.

When people (or mice) suffer heart attacks, SPARC levels are known to rise. The protein also appears to be elevated in people with chronic heart dysfunction. Predicting that SPARC provides a protective service to hearts trying to heal, the authors overexpressed SPARC after heart injury in normal mice. As expected, mice with more SPARC survived longer. In nonheart cells, SPARC amplifies signals induced by TGFβ, a cytokine with known heart-healing properties. Indeed, treating SPARC-deficient mice with TGFβ rescued collagen deposition and hastened healing.

Whether SPARC expression varies in humans has not yet been examined, but low levels could be an underlying factor in heart recovery. And as matrix proteins tend to decrease over time, diminishing SPARC expression may help explain why the elderly suffer higher rates of mortality after heart attacks. The authors suggest that in the future, treating people with recombinant SPARC might help heart attack victims recover.

Snail silences suppressor

The Snail protein has a new carcinogenic trick up its sleeve, according to Massoumi et al. on page 221.

In many different types of cancer, the transcriptional repressor Snail helps tumors spread by dampening the expression of the sticky E-cadherin molecules that hold adjacent cells together. Now, Massoumi et al. show that Snail also promotes tumor cell division by shutting off the tumor

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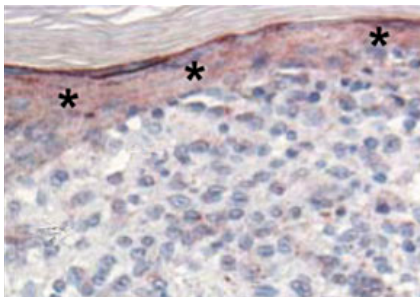
suppressor CYLD. When Snail was blocked in melanoma cells, the low CYLD expression bounced back, and the cells formed smaller and less aggressive tumors when transferred into mice.

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.



Downregulation of the tumor suppressor, CYLD (red, asterisks), contributes to malignant melanoma.

Soothing baby's skin

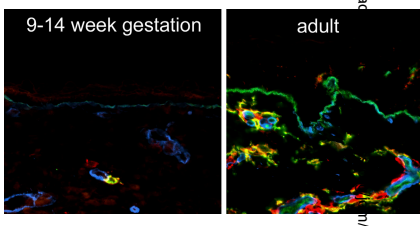
It's not ineptitude that keeps immune cells in human embryonic skin from reacting to motherly tissue. According to Schuster et al. on page 169, the cells are suppressed from the get-go.

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.



Antigen-presenting cells (yellow) in the skin begin to form during the first trimester.

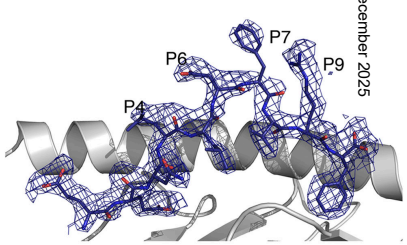
Accounting for taste

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 B*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.



A conformational change allows T cell receptors to attach more firmly to an EBV peptide bound to HLAB*4405.