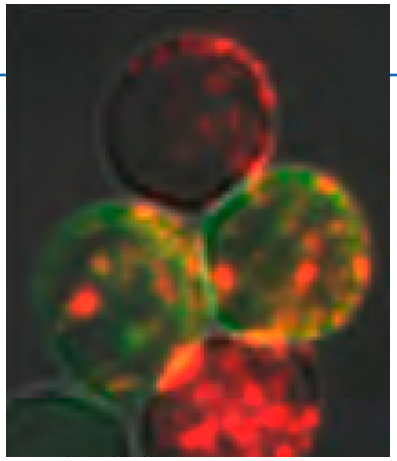
The secret autoreactivity of B cells



A surprisingly large number of B cells express two different Ig light chain alleles (red and green).

Like the proverbial wolf in sheep's clothing, B cells can hide the fact that they are harboring a dangerous autoreactive immunoglobulin (Ig) by displaying a second innocuous Ig. Casellas et al. (page 153) now reveal how these fluffy white villains come to exist and, rather worryingly, that there are potentially large numbers of them in our system.

Transgenic B cells forced to express one self-reactive Ig allele can switch on a second nonautoreative Ig in a process called allelic inclusion. This second Ig appears to dilute the autoreactive potential of the cell. But it is unknown whether allelic inclusion, which defies the "one lymphocyte–one antibody" theory of B cell specificity, can occur under normal physiological conditions.

Using physiologically normal mice that carried one human and one endogenous allele of the Ig light chain gene (to enable identification of both), Casellas et al. discovered that approximately 10% of B cells express two Ig light chain alleles.

The coexpressing cells might arise either because allelic exclusion—the permanent switching-off of one allele—fails or because the second allele gets switched on during receptor editing. Such editing, which occurs if the first Ig produced by a B cell is discovered to be autoreactive, involves switching back on the machinery necessary for Ig gene recombination and expression. With this machinery back on, the second allele might get activated.

Consistent with this hypothesis, coexpression and autoreactivity were correlated. The team also sequenced the Ig genes in coexpressing cells and found strong evidence that editing had occurred. The developmental path of these coexpressing cells was slower than that of monoexpressing cells, consistent with a necessary pause for editing.

The coexpressing B cells, though large in number, appear to have their autoreactive tendencies tempered by the second Ig allele. However, B cells undergo somatic hypermutation at their Ig genes during an immune response, suggesting that autoimmune disease might be triggered if the innocuous allele is edited into oblivion and the wolf is let loose. JEM

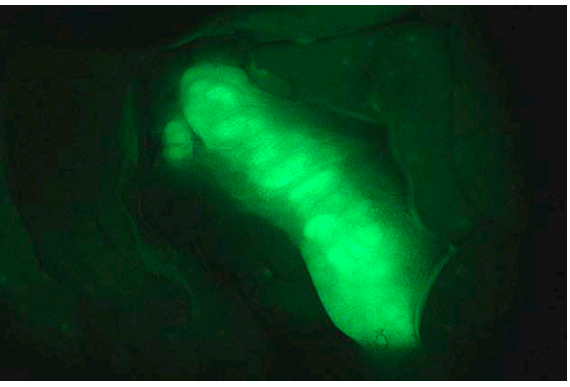
Cell replacement therapy—are MAPCs the answer?

Inherited blood disorders could be a thing of the past. Serafini et al. report on page 129 that multipotent adult progenitor cells (MAPCs), produced in vitro from bone marrow, have blood-building capacity in immune-deficient mice.

The full complement of blood cell types arises from hematopoietic stem cells (HSCs) of the bone marrow. The ability of these cells to both self-renew and to produce daughter cells capable of any hematopoietic fate makes them an attractive resource for cell replacement therapy for blood and immune disorders. However, as with adult stem cells from other tissues, long-term culturing of these cells has proven difficult.

MAPCs, on the other hand, can divide seemingly endlessly in culture. These cells, which can give rise to multiple cell types, were discovered by chance when Catherine Verfaillie's group was trying to culture another type of adult stem cell. The group now shows that MAPCs can reconstitute hematopoietic compartments in vivo just as well as HSCs. Indeed they can even give rise to HSCs themselves.

The team irradiated mice to knock out their immune cells and then injected traceable MAPCs. MAPC-derived cells were detectable in the bone marrow, spleen, peripheral blood, and lymph nodes of recipient mice and expressed appropriate B, T, and myeloid cell surface markers. Furthermore, MAPC-derived B and T cells were shown to be functional by their production of immunoglobulin and response to T cell receptor stimulus, respectively.



MAPC-derived cells (green) restock the lymph nodes of an immunocompromised mouse.

The team showed that MAPCs also gave rise to functional long-term HSCs. Transfer of bone marrow cells from the primary recipient mice into new irradiated mice once again led to hematopoietic reconstitution, as did a third round of transfer from these secondary mice to tertiary recipients.

None of the recipient mice in the study developed tumors, even though some of the MAPCs they received were genetically abnormal because of long-term culturing. Genotyping of the recipients' peripheral blood revealed normal karyotypes, leading Verfaillie to suggest that the genetically abnormal MAPCs were somehow cleared by the body.

The risk of tumor development from transplanted embryonic stem cells (ESCs) is an ongoing concern for their use in therapy. The potential of long-term culture followed by tumor-free cell transfer thus gives MAPCs a therapeutic advantage over both ESCs and HSCs. JEM

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Targeting AID

A dangerously mutagenic protein is targeted to a single genomic site by ssDNA, report Ronai et al. (page 181).

High frequency mutation at the immunoglobulin V region improves antibody affinity and specificity as part of the adaptive immune response. AID (activation-induced cytidine deaminase), which converts deoxycytidines to deoxyuridines, initiates this mutation process. These conversions then induce various error-prone repair mechanisms, increasing the mutation rate further.

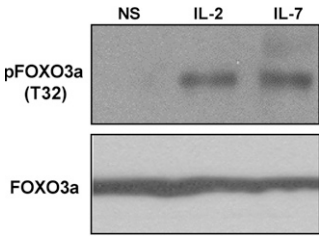
AID must be targeted carefully, however, as it is a potent mutagen. Indeed mistargeting of AID-induced mutations is thought to cause B cell lymphomas.

AID's only in vitro substrate is ssDNA. The team isolated chromatin from B cells undergoing somatic hypermutation (SHM) and found that chromatin- and transcription-dependent ssDNA was present at V regions.

Many genes in B cells are highly transcribed, but the team found that such loci had much less ssDNA than those undergoing SHM. The ssDNA may be short lived during normal transcription but persist at V regions, perhaps due to RNA pol II pausing. Whatever the reason, it seems that the specific abundance of ssDNA at the V region might be one of the chromatin signals for targeting AID. JEM

Memory maintenance

T cells that remember a previously encountered virus are essential in establishing protective immunity. But some T cells have a longer lifetime, and thus effectively a longer immunological memory, than others. Work by Riou et al. (page 79) might explain why effector memory T cells (T_{EM}) are short lived, whereas central memory T cells (T_{CM}) are maintained in the body long-term.



IL-2– and IL-7–induced phosphorylation of FOXO3a (top) may promote survival of T_{CM}.

The longer-lived T_{CM} mainly reside in secondary lymphoid organs such as the lymph nodes, whereas the T_{EM} are found in the peripheral tissues and sites of infection. The exact ontogeny of the two cell types is unknown, but it's thought that T_{CM} might give rise to the more transient T_{EM} fighters. Regardless of origin, the biological basis for their different life spans was unknown.

Dendritic cells (DCs) were a good starting point, as they are known to produce the T cell survival factor IL-7. The team added dendritic cells to the two memory cell populations and found that the T_{CM} proliferation response was more vigorous, perhaps because IL-7 (and IL-2) more efficiently activated the pro-survival factor STAT5 in T_{CM}.

Even without DCs, T_{CM} were less susceptible to apoptosis. These cells had less active pro-apoptotic transcription factor FOXO3a and lower transcription of its targets. FOXO3a activity is inhibited by phosphorylation, and adding IL-7 or IL-2 to the T_{CM} increased FOXO3a phosphorylation at a particular residue, suggesting these cytokines might promote the long-term survival of T_{CM} by both increasing proliferation and decreasing death. JEM

Activating autoimmunity

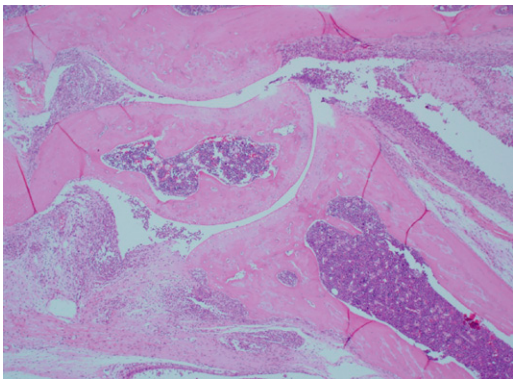
Why the body is sometimes attacked by its own immune system is largely a mystery. Work by Hirota et al. (page 41) suggests how an underlying genetic predisposition might combine with an environmental factor—specifically, an unrelated infection—to give rise to rheumatoid arthritis (RA) and possibly other autoimmune disorders.

A mouse model for RA, called SKG, has a single mutation in the ZAP-70 gene that causes an abundance of highly self-reactive T cells to enter the circulation. In a pathogen-free environment these mice are healthy, but when exposed to pathogens the mice develop autoimmune arthritis.

When these mice start to mount an immune response, such as that induced by a pathogen, their antigen-presenting cells (APCs) increase production of the IL-6 cytokine, the team shows. This IL-6 triggers the T cells to proliferate rapidly and differentiate into Th17 cells, which produce vast amounts of the proinflammatory cytokine IL-17. SKG mice that lacked either IL-17 or IL-6 were protected from arthritis.

Some potentially arthritogenic Th17 cells already exist in the pathogen-free mice due to the constant interaction between APCs and T cells. Activation of the Th17 cells is minimal without pathogen, but an increase in IL-6 during an immune response to a microbe, coupled with the constant exposure to self antigens, is just enough to tip these precariously balanced T cells into overdrive.

IL-17 levels have been shown to be high in a number of autoimmune disorders, including RA. Furthermore, mutation of a protein in the same pathway as ZAP-70 is a common genetic risk factor for RA. It is possible, therefore, that similar genetic and environmental factors also come together to produce RA in humans. JEM



Pathogens encourage the production of self-reactive T cells, which cause autoimmune arthritis (purple, infiltrating cells).