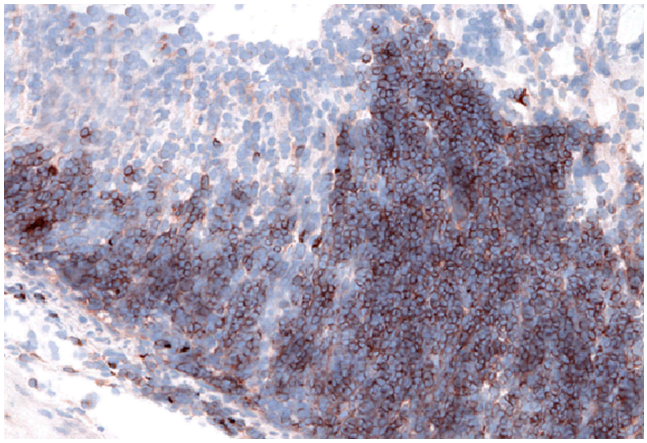


IgM+ B cells (brown) develop in the mouse gut even when the spleen and gut lymphoid tissues are missing.

Gut-friendly B cells?

On page 1343, Shimomura et al. identify a group of B cells that rebels against convention: unlike other B cells, this group matures in the gut and might protect it from inflammatory damage.

B cells are thought to mature in the bone marrow and spleen. As they mature, B cells express the immunoglobulin receptor IgM, which distinguishes them from their antigen-activated brethren. The activated cells are mostly found in gut lymphoid tissues, where they secrete antibodies.

The mouse gut, however, also contains IgM+ B cells, which increase in number during inflammation. These cells were assumed to be either antigen-inexperienced cells that were just passing through or antigen-activated immigrants that hadn't yet matured.

But Shimomura et al. now find that the gut IgM+ B cells did not express the same pattern of cellular receptors that mark B cells that mature elsewhere, suggesting that that these cells may be long-term gut residents. The authors found IgM+ gut cells in mice that lacked spleens, gut lymphoid tissues, or inflammation—conditions that deter activated B cells from entering and surviving in the gut.

The cells also differed from other B cells in their ability to survive in the absence of antigen. They only needed the cytokine BAFF, which helps B cells transit through developmental checkpoints. And although the IgM+ cells multiplied during inflammation, the expanded population included a diversity of clones instead of a narrow, antigen-specific repertoire.

The function of these cells is still unclear, but the study offers some clues. The cells expanded only as the inflammation was dying down, and in response to innate immune receptor activation, they secreted IL-12—a cytokine that tempers chronic gut inflammation. The authors propose that these IgM+ B cells, which can also produce the suppressive cytokine IL-10, may be the precursors of regulatory B cells previously associated with chronic gut inflammation. JEM

Balanced T cell subsets for good health

On page 1381, Lochner et al. expose the promiscuity of a transcription factor that was previously thought to be exclusive to inflammatory T helper (Th) 17 cells. They now find that this protein is also expressed by a group of regulatory T (T reg) cells that keeps Th17 cells in line.

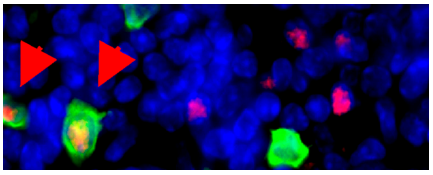
Both cell types stem from naive CD4+ T cells, depending on the cytokines in attendance: T reg cells are induced by high levels of TGF-β, whereas inflammatory Th17 cells are induced by lower levels of TGF-β and IL-6. Each subset foils the other by secreting cytokines with opposite functions. When T reg cells are missing, mice have more Th17 cells and develop inflammatory diseases, suggesting that one subset might limit the other to maintain health.

Th17 cells were previously detected based on their expression of the transcription factor RORγt, which is required for their development. But Lochner et al. now find that in healthy mice, the RORγt+ T cell population includes a group of cells that does not produce the signature Th17 cytokine IL-17 when activated. These cells instead secreted the suppressive cytokine IL-10 and expressed the T reg cell–specific transcription factor Foxp3 alongside RORγt.

These RORγt-expressing T reg cells expressed ligands for chemokine receptors found on Th17 cells. Mice that lacked these receptors had more Th17 cells, suggesting that the T reg cells might lure the inflammatory cells into a suppressive environment.

The T reg cells also controlled their nemeses in a more direct way. In RORγt+ T reg cells, RORγt was bound by Foxp3, suggesting that Foxp3 may actively derail Th17 development. Consistent with this idea, naive CD4+ T cells cultured with TGF-β alone first expressed RORγt and later expressed Foxp3, which drove them to become T reg cells. The delayed induction of Foxp3 could be prevented by IL-6, thus freeing RORγt to drive Th17 differentiation. Whether suppressive cytokines can reverse this switch is yet to be determined.

Both RORγt-expressing populations were present in equal numbers in most tissues of healthy mice, suggesting mutual control between the two cell types. Both populations expanded proportionally in response to inflammation or infection, which is probably important to ensure a damage-free recovery. JEM



The naive RORγt+ T cell population (green) includes Foxp3-expressing regulatory T cells (arrowheads).

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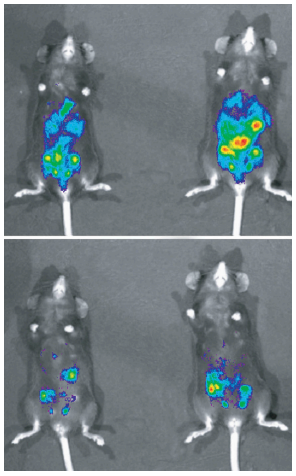


Ovarian tumors (blue) are destroyed in mice injected with macrophages in which IKKβ signals are inhibited (bottom).

Retraining macrophages to kill tumors

Some tumors avoid getting killed by turning macrophages into immune-suppressive cells. Hagemann et al. (page 1261) now find that these impotent cells can be reverted into weapons of tumor destruction by simply suppressing a kinase.

Macrophages can destroy tumor cells by producing inflammatory molecules. But macrophages within tumors often secrete harmless antiinflammatory cytokines and proteins that promote tumor growth. Tumor cells induce this transformation, but the signals that drive the conversion were unknown.

Hagemann et al. now find that tumor macrophages in mice are disarmed by signals that activate NF-κB—a transcription factor that normally drives inflammation. As in inflammation, tumor macrophage NF-κB was turned on by IκB kinase (IKK) β. In tumors, however, IKKβ also suppressed STAT1—a transcription factor that turns on tumor-fighting genes. The basis for this difference is unclear. Perhaps the tumor contains unique cues that instruct the IKK pathway to shut off STAT1.

STAT1 suppression in macrophages depended solely on the cytokine receptor IL-1R and its downstream adaptor, MyD88, suggesting that tumors might protect themselves by secreting the IL-1R ligand, IL-1β. Macrophages from tumors or from healthy animals became in vivo tumor killers when engineered to express dominant-negative IKKβ. These reprogrammed macrophages produced high levels of IL-12, which recruited tumor-fighting NK cells. The group is now investigating whether infusing similarly reprogramed macrophages into cancer patients will help reverse tumor growth. JEM

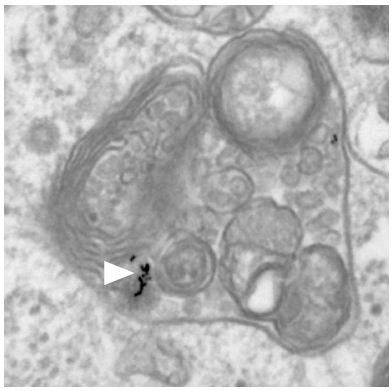
No exit strategy for lipids

Lipids heading toward lysosomes that carry a mutated ion channel are spared from destruction, according to Meidel et al. (page 1477). The accumulating undigested fat eventually dooms the cell.

Cells get rid of excess fat, which comes from worn-out organelles or engulfed pathogens by, for instance, shuttling them in endosomes to degradative lysosomes. The two organelles are thought to fuse when the lysosomal ion channel TRP-ML1 lets in calcium.

Individuals with mutated TRP-ML1 suffer from a fatal disease called mucolipidosis type IV, which is characterized by fat accumulation in tissues. The failure of endosomes to fuse with lysosomes in these patients' cells, as seen in previous imaging studies, was thought to cause the fat pile up and trigger disease. But because TRP-ML1 also lets through protons, which lowers the pH and thus activates lysosomal enzymes, Meidel et al. wondered whether the fat backlog is caused by a degradation defect rather than a fusion failure.

By silencing TRP-ML1 in normal cells, the group now shows that the channel is not necessary for fusion. In its absence, however, lysosomes became overacidified and thus failed to process their lipid load. The pH defect suggests that the channel leaks protons out of the lysosome to prevent the interior from becoming too acidic. Lipid-clogged lysosomes might send feedback signals that prevent them from taking on new cargo. JEM



Lysosomes (arrowhead) in TRP-ML1–deficient cells internalize endosomal cargo (spots) but fail to degrade it.

Endothelial cells instigate sepsis

During severe bacterial infections, the transcription factor NF-κB is both an asset and a liability. On page 1303, Ye et al. show that its activation in endothelial cells singlehandedly perpetuates the inflammation that drives septic shock.

NF-κB is required in endothelial cells for new blood vessels to grow. And in immune cells, its activation is essential for defense against bacteria and other infectious agents. Blocking NF-κB in mice, for example, turns a normally manageable infection deadly. But more selectively inactivating the protein has proven beneficial in other systems, including certain cancer models.

Following this lead, Ye et al. disabled NF-κB activation only in endothelial cells. The resulting mice survived a normally lethal bacterial infection and avoided septic shock. Being free of active NF-κB allowed the endothelial cells lining blood vessels to maintain their cell–cell junctions and minimize their stickiness, thus limiting the fluid leakage and massive immune cell infiltration into tissues that triggers shock.

Thus, NF-κB–driven activation of endothelial cells, not immune cells, seems to be the driving force behind the escalating inflammation that causes sepsis. JEM