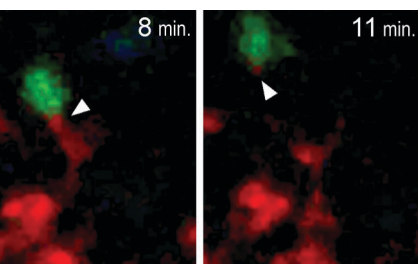




Agricultural pesticides may drive the proliferation of potentially carcinogenic B cell clones.

WOLFGANG SCHLEGEL



A naive B cell (green) captures antigen (red) from an FDC.

Pesticide-induced proliferation

Pesticide exposure may contribute to cancer by causing genetic mutations during B cell development. On [page 1473](#), Agopian et al. show that pesticides also increase the rate of precancerous B cell proliferation.

Follicular lymphoma is a B cell cancer characterized by a translocation event that occurs as activated B cells undergo AID-driven diversification of their antibody genes in germinal centers (GCs). This translocation, known as t(14;18), links the gene encoding the pro-survival protein BCL2 to the heavy chain locus (IgH) resulting in aberrant BCL2 expression and cell survival. These translocations can also be found in healthy individuals, indicating that additional cancer-causing events are required to cause disease.

This group previously found that farmers exposed to pesticides have increased numbers of t(14;18)-positive B cells in circulation. And pesticide exposure has been associated with increased risk of developing t(14;18)-positive follicular lymphomas. But exactly how pesticides promote lymphoma was unclear.

By following the same group of pesticide-exposed farmers over a decade, the authors now find that pesticide-exposed farmers accumulated t(14;18)-positive B cells faster than their nonexposed neighbors. The t(14;18)-positive cells were mainly clones of a few types, however, which indicated that pesticides were promoting B cell expansion more than they were directly causing DNA damage. How pesticides trigger proliferation remains unknown.

Whether from pesticide-exposed or unexposed individuals, the circulating t(14;18)-positive B cells derived from GC—as indicated by ongoing AID activity and expression of the GC marker CD10—and constituted bona fide precursors of follicular lymphoma cells. The continuous AID activity correlated with numbers of translocation-containing B cells, providing a clue about how the rapidly proliferating cells may parlay disease. Subsequent mutations triggered by AID-driven breaks and misrepair could result in lymphoma. In future surveys, the authors hope to pinpoint what puts certain t(14;18)-bearing individuals at greater risk for developing cancer.

Spying on antigen hand-offs

On [page 1485](#), Suzuki et al. catch naive B cells snatching antigens from follicular dendritic cells (FDCs) on film—or rather, on a hard-drive recording lymphoid follicles in real time. The interaction between these cells had been inferred for many years, but modern visualization tools had not yet been used to investigate the details of antigen capture.

A critical step in adaptive immunity occurs as B cells acquire antigens, proliferate, and differentiate within lymph nodes. FDCs aid this process by extending their long processes through lymphoid follicles, capturing antigens (together with complement) as they enter, and presenting them to naive B cells. Here, Suzuki and colleagues document B cell–FDC interactions from start to finish using two-photon microscopy.

The authors' images confirm the reputation of FDCs as enduring antigen presenters. Naive B cells continued to pick up antigens from FDCs nine days after immunization, perhaps increasing the chance that rare or distant B cells will encounter their antigen.

FDCs and B cells spent about 6.5 minutes in contact. And during this period they captured large chunks of antigen, sometimes grabbing bits of the FDC as well. The authors suggest that high affinity B cells take a piece of the FDC in order to increase their antigenic bounty. Indeed, the cells bearing FDC tidbits glowed brightest with fluorescently labeled antigen. Whether the extra baggage alters B cell fate remains to be investigated.

Visualization required the use of high affinity antigen–B cell receptor combos, which are not necessarily the norm during primary immune responses. However, using flow cytometry, the authors confirm that FDCs hand off antigen to low affinity B cells in a similar manner.

IL-17's tumor team

In cancer, tumors may skew a cytokine tug-of-war to favor their own growth and survival, according to Wang et al. on [page 1457](#).

The signature Th1 cytokine IFN- γ is a well-known tumor antagonist that promotes tumor attack by killer T cells and renders tumor cells more susceptible to death. IFN- γ also suppresses the development of IL-17-producing Th17 cells, which have recently been suspected to aid

tumors. Here, the authors find that IL-17 helps tumors grow both by inhibiting Th1 differentiation and activating the oncogenic signaling molecule STAT3.

In mice that lack IL-17, two types of established tumors (melanoma and bladder) grew slowly. Without IL-17, IFN- γ -producing T cells flooded the tumor and stunted its growth. When IFN- γ was missing, Th17 cells won out, allowing tumor growth to skyrocket.

IL-17 activated STAT3 indirectly via the cytokine IL-6. And because IL-6 also promotes Th17 differentiation, the tumor-promoting cycle was amplified. STAT3 drove the expression of target genes that promote cell survival, proliferation, and angiogenesis. In this way, tumor growth was also attenuated by blocking IL-6 signals.

Both tumor cells and surrounding endothelial cells responded to IL-6, but the endothelial cells had more activated STAT3. Senior author Drew Pardoll points out that the contribution of cells around the tumor may vary among cancers. Some tumors, for example, could be surrounded by cells bearing fewer IL-6 receptors than those studied here. “It’s an elegant notion that the Th1 pathway produces anti-cancer immunity and the Th17 pathway promotes cancer,” says Pardoll. “I’d be pleasantly surprised if in the end it really is that simple.”

Healthy hearts lay off LOX

A lipid-busting lipoxigenase (LOX) enzyme triggers cardiac failure by luring troublemaking macrophages into the heart, according to Kayama et al. on [page 1565](#).

Heart failure commonly follows heart attack, chronically high blood pressure, and heart disease. And macrophage build-up appears to accompany those conditions as they worsen. Here, Kayama and colleagues find that the enzyme 12/15-LOX is dramatically upregulated in the failing hearts of rodents, where it stimulates a macrophage attractant.

Mice whose hearts expressed excess 12/15-LOX accumulated macrophages and developed problematic pumping and cardiac fibrosis that eventually led to heart failure. Increased LOX activity boosted levels of the macrophage attractant MCP-1, and blocking MCP-1 signals reduced macrophage accumulation and restored normal heart function. The connection between the LOX and MCP-1 could also account for the enzyme’s role in other heart disorders such as atherosclerosis.

LOX induces MCP-1 by metabolizing arachidonic acid into byproducts such as 12-HETE. This process occurred in cardiomyocytes, but the metabolite appears to trigger MCP-1 production by other heart cells. Fibroblasts and endothelial cells—but not cardiomyocytes—produced MCP-1 when treated with 12-HETE in vitro.

High cardiac pressure may call LOX into action suggest the authors, as inducing aortic constriction in another mouse model caused LOX activity and 12/15-HETE levels to increase.

Mend that gut, STAT!

Deep in the gut, STAT3 applies Nature’s band aid. According to Pickert et al. on [page 1465](#), the signaling protein heals wounded intestines and promotes recovery after colitis.

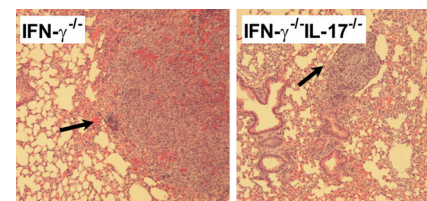
Eliminating STAT3 from intestinal epithelial cells took no toll on mice until they were treated with the colitis-inducing irritant DSS. While normal mice recuperated after the treatment, those that lacked epithelial STAT3 had problems recovering.

They continued to suffer weight loss, severe tissue damage, and intestinal bleeding after the treatment stopped. Healing required secretion of the cytokine IL-22 from local dendritic cells, which was needed to activate STAT3.

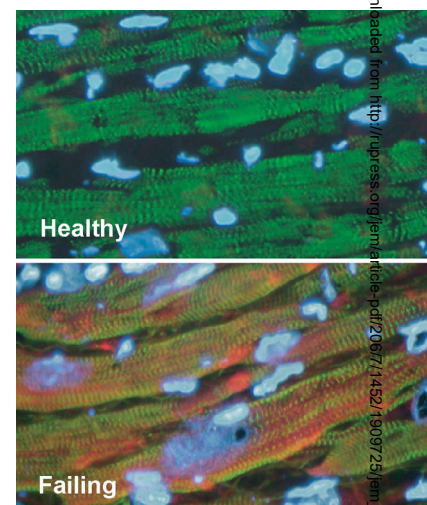
Depending on the disorder, IL-22 and STAT3 can be helpful or harmful. IL-22 exacerbates autoimmunity and STAT3 participates in tumor growth. Other studies suggest that IL-22 protects patients with IBD, perhaps by stimulating the production of antimicrobial peptides.

Here, STAT3 promoted cell growth just as it does when aiding colitis-associated tumors: it prevented the death of epithelial cells around a wound by downregulating death-promoting genes and induced healing with proliferation-inducing genes. Because of its tumor-enhancing tendencies, therapeutic activation of STAT3 in colitis patients must be approached cautiously.

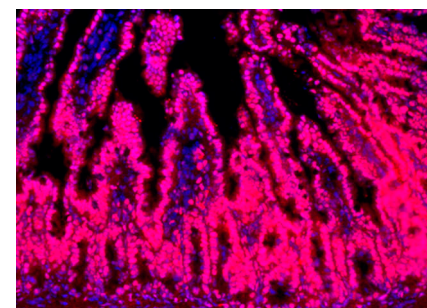
A polymorphism in STAT3 was recently linked to colitis in humans. Perhaps this, or some other mutation, disrupts STAT3 expression, leaving the person vulnerable to intestinal disorders following infection or injury.



Without IL-17, STAT3 levels drop, slowing tumor growth and spread (arrows).



Failing hearts upregulate 12/15-LOX (red) in cardiomyocytes (green).



STAT3 (red) helps wounded intestines heal.