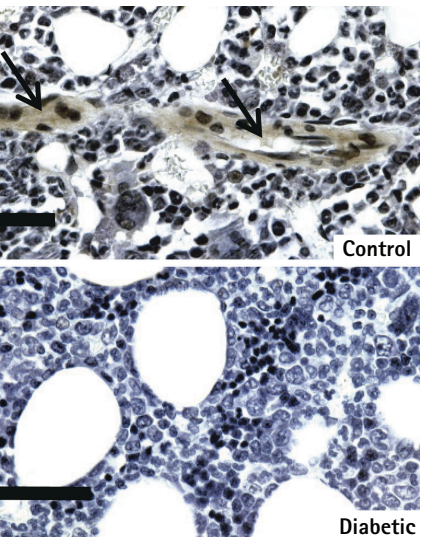
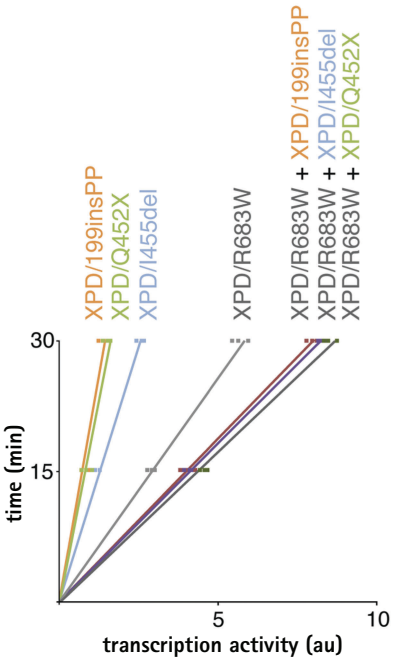


Bone marrow nerves (arrows) are damaged in diabetic rats, stunting the ability of reparative progenitor cells to exit into circulation.



Mutations in XP patients affect gene transcription in different ways.

Crippled clock hinders healing

Diabetic eye damage may start in bone marrow, suggest Busik and colleagues. Damaged bone marrow nerves and disrupted circadian genes hampered the release of progenitor cells that are required to repair diabetes-induced vessel injury in the eye.

Up to 45% of diabetic adults in the US develop retinopathy, a potentially blinding condition. Although high glucose levels and oxidative stress may cause the initial eye injury, Busik et al. suggest that the inability to repair damage causes the real problem. Normally, endothelial progenitor cells (EPCs) exiting the bone marrow help to regenerate damaged vessels during sleep. This nocturnal EPC egress is faulty in patients with diabetes, creating abnormally low levels of nighttime EPCs. Here, the authors show that diabetic rats have similar EPC deficits during the day when they normally sleep.

Diabetic rats showed signs of damage to bone marrow nerves, which trigger the signals required for EPC exit. Nerve damage coincided with a drop in the expression of circadian "clock" genes that control the ebb and flow of EPC migration. With fewer reparative EPCs on the move, damaged eye vessels accumulated in diabetic animals. Circadian rhythm disruption has also been blamed for the glucose and blood pressure complications characteristic of diabetes.

Because nerve damage and clock gene irregularities preceded eye disease, the authors suggest that the resulting EPC malfunction leads to retinopathy. What triggers nerve damage and circadian disruption is not yet known. Senior author Maria Grant suspects a role for nitric oxide, a known regulator of circadian gene transcription that is commonly elevated in patients with diabetes.

XP mutant power!

Patients with the DNA-repair disorder xeroderma pigmentosum (XP) suffer from a wide range of symptoms; some are mild, such as excessive freckling after sun exposure, whereas others are more severe, including skin cancer and neurodegeneration. Genetic variation underlies this heterogeneity, argue Ueda and colleagues.

The so-called "causative" XP mutation (R683W) lies within the transcription complex TFIIH, which helps to transcribe nearly all genes and to repair damaged DNA. The complex includes three subunits with separate enzymatic functions. The R683W mutation is in the XPD subunit and disrupts helicase activity.

XP patients can be homozygous or heterozygous for the R683W mutation. And some heterozygotes bear secondary mutations on the opposing XPD allele. Contrary to popular belief, Ueda et al. suggest that these additional mutations matter. Patients with different secondary mutations had different XP symptoms. And their secondary mutations had a variety of molecular outcomes, ranging from the deletion of an amino acid to the production of a truncated protein.

The authors found that different allelic combinations interfered with TFIIH's repair and transcription cascades in unique ways. Some combinations hampered DNA repair by weakening a link between XPD and another subunit of TFIIH, which decreased XPD's helicase activity. Other mutations indirectly disturbed the function of kinase required for the phosphorylation and activation of RNA polymerase II.

Ueda and colleagues thus suggest that secondary XPD mutations can either enhance or counteract clinical symptoms. Exactly how the nuances in XPD function dictate specific symptoms is not yet clear, and many more XPD mutations remain to be investigated.

Regulating the regulators

An inhibitory receptor–ligand pair does more than stifle immune responses—it helps the cells that stifle immune responses, report Francisco and colleagues.

Regulatory T (T reg) cells halt aggressive immune responses before they cause damage. But too many T reg cells can obstruct a needed response against cancer or infection. Now, Francisco et al. reveal that the inhibitory programmed death (PD) 1 pathway, known to induce tolerance, promotes T reg cell activity by stimulating and maintaining the expression of Foxp3, the signature T reg cell transcription factor.

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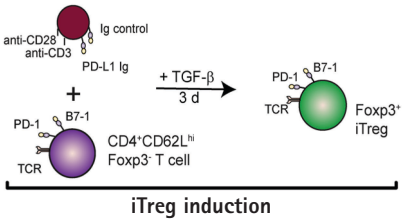
In mice lacking PD-ligand (PD-L) 1 and PD-L2, transferred T cells failed to convert into T reg cells, and the mice quickly succumbed to inflammatory disease. Factors like TGF-β, IL-2, and Runx3 also help trigger and maintain T reg cells. PD-L1 augmented TGF-β signals, but also stimulated Foxp3 on its own. The authors also show that PD-L1 biased the differentiation of naive T cells toward a T reg cell fate by obstructing the Akt-mTOR signaling pathway required for effector T cell survival.

The PD-1 pathway keeps inflammation in check, the authors say. Inflammatory cytokines drive PD-1 expression, which in turn triggers T reg cells that dampen the inflammation. Manipulating this balance has been a long-standing therapeutic goal. Indeed, PD-1 and PD-L1 inhibitors are in clinical trials as anticancer agents. Francisco et al. suggest that PD-1 and PD-L1 agonists could also be used for the opposite effect—to sustain T reg cell function during organ transplantation or autoimmunity.



iTreg induction

Co-culture of PD-L1–expressing beads (red) and naive T cells (purple) promotes their conversion into T reg cells (green).

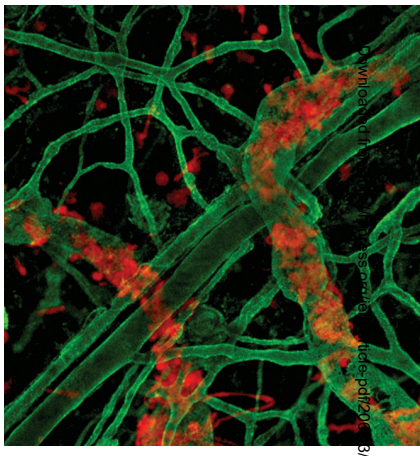
Poking through lymphatic portals

Dendritic cells (DCs) creep like amoebas into lymph vessels. Pflicke and Sixt catch them squeezing through minute pores and trap doors to enter.

Two barriers surround vessels—the endothelium and the basement membrane. Leukocytes use integrins and proteases to adhere to and drill through blood vessel walls as they exit. Entrance into lymph vessels, however, is mysteriously different because it requires neither tool. To figure out how leukocytes barge in, Pflicke and Sixt used live cell imaging to follow DC migration in explanted skin from mouse ears.

A close look at the lymphatic basement membrane revealed periodic perforations. DCs squeezed through these holes by inserting projections and then swelling until the gaps widened enough for the cell bodies to slip through. At the next barrier, the lymphatic endothelium, the cells took advantage of flexible oak leaf–shaped junctions, which are known to flap open in only one direction, allowing the cells in but not out.

This manner of DC lymphatic travel may not apply outside of the afferent lymphatic system because not all linings bear pores or hinge-like junctions. Entering and exiting blood vessels, for example, might be more restricted because blood vessels must be tightly sealed against fluid leaks. Nonetheless, lymphatic migration is far from free-form. Visualizing the chemokine gradients that likely steer DCs into and around lymphatic vessels is the team's next challenge.



Dendritic cells (red) enter lymphatic vessels (green) through perforations in the basement membrane.

Inflammation stops at Bop

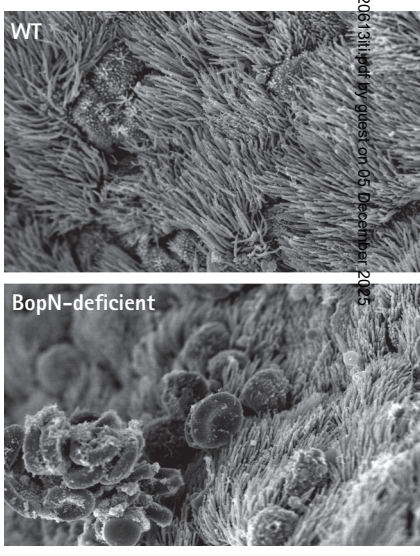
Bordetella, the pathogen underlying whooping cough, short-circuits the host immune response by triggering the antiinflammatory cytokine IL-10. Now, Nagamatsu and colleagues nab the bacterial protein that does the job.

Bacteria often thwart inflammatory responses by injecting effector proteins into host cells through a syringe-like organelle called the type III secretion system (T3SS). These effector proteins manipulate the host immune response in a variety of ways. Here, Nagamatsu et al. discover the first bacterial effector protein known to trigger IL-10.

Bordetella secretes at least two T3SS effector proteins into host cells, BopC and BopN. BopC induces cell death, and BopN is now shown to trigger IL-10 when it moves into the nucleus of dendritic cells and macrophages. BopN inhibited MAP kinase signaling and activated the transcription factor SP-1, which is known to promote IL-10 production. BopN also induced NF-κB p50 translocation at the expense of p65, a situation that may also promote IL-10 production.

Mice infected with a BopN-deficient strain of *Bordetella* produced less IL-10, effectively recruited neutrophils to the site of infection, and rid themselves of the bug. Mice lacking IL-10 cleared infection whether or not BopN was intact. And exposing mice to the BopN-deficient strain protected them against later challenge with wild-type bacteria, perhaps by ramping up the production of the inflammatory cytokine IFN-γ.

Because MAP kinase and NF-κB signaling control the expression of thousands of genes, BopN might alter other cytokines as well. A prior study showed that an unidentified *Bordetella* T3SS protein shuts down IFN-γ production. Whether this was a result of IL-10 suppressing IFN-γ–producing cells, of BopN altering NF-κB activation, or the action of a different effector protein altogether remains to be seen.



Infection with BopN-deficient *Bordetella* results in increased inflammation but also in enhanced clearance of infection.